# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 201657Orig1s000

# PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

**Memorandum**

**Date: November 7, 2011**

| | |
|---|---|
| To: | NDA 201-657/Hospira paracalcitol |
| From: | Karen Davis-Bruno PhD; Pharmacology Supervisor; DMEP |
| Subject: | Supervisory Pharmacology/Toxicology Memo |
| Reviewed Materials: | NDA 201-657 Pharmacology/Toxicology Review Parvaneh Espandiari PhD |

NDA 201-657/paracalcitol was submitted as a 505(b)2 application by Hospira for injection (2,5 µg/ml) for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis. The listed drug in the FDA's Orange Book is Zemplar (paracalcitol) manufactured by Abbott. A 4-week intravenous rat toxicity study with a 2-week recovery period comparing Hospira's and Abbott's paracalcitol products was performed in order provide a bridge to Zemplar. This nonclinical study is the only bridge provided between the products. While the active ingredient (b) (4) formulations differ in that Zemplar contains 20% (b) (4) and 30% propylene glycol and the new paracalcitol product by Hospira contains 40% (b) (4) and 10% propylene glycol. The Pharmacology/Toxicology reviewer suggests that the increased (b) (4) concentration in Hospira's paracalcitol may affect the toxicity profile compared to that of Zemplar.

The primary review indicates that Hospira's formulation with two-fold higher (b) (4) and 1/3 the propylene glycol concentration of Zemplar exhibits a delay in the time-course of appearance of soft tissue mineralization as well as increased severity scores for mineralization compared to Zemplar. Injection site histopathology findings differ between the listed paracalcitol and Hospira's product in an inconsistent manner. This memo is designed to discuss the observed differences between the products (delayed and increased severity of soft tissue mineralization; injection site histopathology) and their potential clinical relevance.

## Product Related Differences in injection site histopathology

Injection site effects characterized as endothelial hyperplasia, mural thrombus formation and chronic inflammation were observed in the rat abdominal aorta. The sponsor did not systematically evaluate the low dose paracalcitol or Zemplar vehicle control animals. This was confirmed in a Tcon held with Hospira and DMEP on 10/13/11. The incidences presented by Hospira represent ad hoc analysis presumably based on macroscopic findings leading to histopathology evaluations based on relatively few animals. If the injection site histopathology



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were due to the elevated [(b) (4)] in the Hospira formulation, it would be anticipated that the incidences in the Hospira vehicle, and Hospira 10 µg/kg/day paracalcitol treated groups would be similar whereas the Zemplar 10 µg/kg/day group would be lower than the other groups because of the lower [(b) (4)] content in the Zemplar formulation. However the incidence in the Zemplar treatment group is not consistently lower and the absence of systemic evaluation of the Zemplar Vehicle containing 20% [(b) (4)] (lower [(b) (4)] compared to 40% in the Hospira product) was not performed making this assessment incomplete. Injection site histopathological findings differed between the Hospira and Zemplar products in an inconsistent manner as seen in the table below.

| Injection Site Histopathology Incidence 4-Week Rat | | | | | | |
|---|---|---|---|---|---|---|
| Groups | Endothelial Hyperplasia | | Mural Thrombus | | Inflammation Chronic Vessel Wall | |
| | M | F | M | F | M | F |
| **Hospira** | | | | | | |
| Vehicle Control (40% [(b) (4)] | 5/10=50% Min-mild | 7/10=70% Min-mild | 7/10=70% Min-severe | 2/10=20% Minimal | 3/10=30% Mild-mod | 4/10=40% Minimal |
| Paracalcitol 1.5 µg/kg/day | NA | 2/4=50% | 4/4=100% | ¾=75% | NA | NA |
| Paracalcitol 10 µg/kg/day | 5/10=50% Minimal | 4/10=40% Min-mild | 5/10=50% Min-mod | 6/10=60% Min-mild | 6/10=60% Min-mild | 1/10=10% Mild |
| **Zemplar** | | | | | | |
| Vehicle Control (20% [(b) (4)] | 0/7=0% | 2/4=50% | 6/7=85% | 2/4=50% | 1/7=14% | 2/4=50% |
| Paracalcitol 1.5 µg/kg/day | 3/6=50% | 1/5=20% | 4/6=66% | 5/5=100% | NA | 1/5=20% |
| Paracalcitol 10 µg/kg/day | 5/10=50% Minimal | 3/10=30% Minimal | 8/10=80% Mild-severe | 5/10=50% Min-severe | 1/10=10% Mild | 2/10=20% Severe |

Min=minimal severity; mod=moderate severity, NA=not assayed, incidence= # rats with finding/# rats examined

The incidence of endothelial hyperplasia in males and females given Hospira paracalcitol was similar or lower than the Hospira vehicle control. The Zemplar low and high dose males show a 50% incidence of this finding which exceeds the Zemplar vehicle control suggesting a drug related effect rather than a formulation (i.e. [(b) (4)] effect. Zemplar treated females have incidences of endothelial hyperplasia below the Zemplar vehicle controls, consistent with ~30% lower paracalcitol AUC compared to males. However the paracalcitol treated group incidence is similar with Hospira or Zemplar products, suggesting that Hospira paracalcitol has no greater safety risk for endothelial hyperplasia than Zemplar. Endothelial hyperplasia incidence is not changed following a 2-week withdrawal of drug. A clear paracalcitol or [(b) (4)] effect on the incidence of endothelial hyperplasia can not be established.

Mural thrombus formation appears increased in high dose Hospira females compared to vehicle control. This effect does not appear to be formulation related since this same observation is not seen in males. The low dose



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paracalcitol treated groups exhibit an incidence that exceeds the vehicle controls, suggesting the lack of a formulation effect despite the very limited number of animals assessed for histopathology in the low dose paracalcitol groups. Furthermore, the Zemplar vehicle control incidence is higher than the Hospira vehicle despite a 2-fold higher (b) (4) content. The effect does not appear to be paracalcitol related either since the incidence in the low dose Hospira and Zemplar is higher than in the 10 µg/kg/day paracalcitol treated groups regardless of the formulation/manufacturer in those limited number of animals that were evaluated. The severity scores are lower with Hospira paracalcitol compared to Zemplar. Mural thrombus incidence does not change following a 2-week drug withdrawal in males. Females given Hospira paracalcitol have a reduced incidence following a 2-week drug withdrawal. Overall the incidence of mural thrombus formation appears quite variable across the treatment groups in the main or recovery portions of the study suggesting the absence of any clear correlation between paracalcitol doses or (b) (4) concentration administered.

Similar variability is seen for chronic inflammation of the rat abdominal aorta (injection site). An increase in the incidence of chronic inflammation is seen in high dose Hospira paracalcitol treated males compared to the vehicle control which is not observed with the Zemplar paracalcitol compared to its control. A comparison of the vehicle controls suggests that the Hospira formulation has a greater incidence than the Zemplar formulation. This suggests a formulation related effect in males which is noted in Dr. Espandiari's review. Paracalcitol treated females show a lower incidence than the corresponding control (Hospira or Zemplar) suggesting the absence of a formulation effect in females. The severity scores suggest less severe inflammation with Hospira compared to Zemplar. The incidence with the low dose groups most likely reflect the small sample size as with the prior histopathology findings discussed above. The recovery group data suggests that the chronic inflammation does not recover in females.

There is a difference in the incidence reported for chronic inflammation at the injection site during recovery in Dr. Espandiari's review compared to the sponsor's Toxicology Tabular Summary. The incidences reported in the primary Pharm/Tox review are taken from the study report histopathology results table and are actually lower incidence than that reported by the sponsor in the Toxicology Tabular Summary which is reproduced below. The analysis described in this memo uses the sponsor's Summary Table below.



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| Injection Site Histopathology Incidence 2-Week Recovery | | | | | | |
|---|---|---|---|---|---|---|
| Groups | Endothelial Hyperplasia | | Mural Thrombus | | Chronic Inflammation Vessel Wall | |
| | M | F | M | F | M | F |
| Hospira Vehicle (40% (b) (4) | 0/5=0% | 1/5=20% Minimal | 1/5=20% Mild | 2/5=40% Moderate | 2/5=40% Minimal | 3/5=60% Minimal |
| Hospira Paracalcitol 10 µg/kg/day | 2/5=40% Min-mild | 1/5=20% Minimal | 2/5=40% Minimal | 0/5=0% | 4/5=80% Min-mild | 4/5=80% Minimal |
| Zemplar Vehicle (20% (b) (4) | NA | 3/3=100% | 2/3=66% | 2/3=66% | 0/3=0% | 1/3=33% |
| Zemplar Paracalcitol 10 µg/kg/day | 2/5=40% Mild | 2/5=40% Minimal | 3/5=60% Min-mod | 4/5=80% Min-mod | 5/5=100% Minimal | 4/5=80% Min-mod |

Min=minimal severity; mod=moderate severity, NA=not assayed, incidence= # rats with finding/# rats examined

Taken together a consistent formulation or paracalcitol related effect on injection site histopathology (incidence or severity) has not been identified. Since the API (b) (4) a drug-related effect would be anticipated to be consistent with paracalcitol treatment. Similarly, a formulation-related effect would be anticipated to be similar between the corresponding vehicle control and paracalcitol treatment based on similar (b) (4) content. However any difference between the Hospira and Zemplar products anticipated to be due to the formulation differences should be similar across genders, which is not observed.

Dr. Espandiari identifies the Hospira Paracalcitol treated male rats as being the dose group expressing an elevation in chronic inflammation of the injection site (abdominal aorta vessel wall) incidence (60%) over the Hospira vehicle control (30%). A similar increase is seen in Hospira high dose treated females (60%) relative to vehicle control (20%) for mural thrombus formation. Among the injection site histopathology findings observed, thrombus formation is perhaps the most clinically relevant to the patency of the A-V fistula which is the site reserved for dialysis in CKD patients. Toxicokinetics reveals greater exposure in males (41%) relative to females. While this might explain the increased inflammation in males it can not explain the observation in mural thrombus formation. The formulations tested in the Hospira treated male and female rats is identical. Therefore the formulation (i.e. (b) (4) can not account for the increases observed.

**Product Related Differences in Soft Tissue Mineralization**

The vehicle control for the Zemplar formulation as well as the low dose groups (1.5 µg/kg/day) for both Hospira and Zemplar paracalcitol treated groups were not evaluated by histopathology. Evaluation of the high dose males (10 µg/kg/day) reveals a delayed appearance of soft tissue mineralization (aorta-thoracic, heart, abdominal regions; stomach, mammary gland and kidney) with Hospira's product compared to the listed drug Zemplar at the same dose. The incidence of tissue mineralization appears in the recovery group animals instead of the main study animals with Hospira, in contrast with Zemplar. The delayed effect may be attributed to the higher (b) (4) in the Hospira formulation compared



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to Zemplar. This potential mechanism will be discussed subsequently in this memo. The overall incidence of this finding in the main and recovery study groups is lower with Hospira's paracalcitol compared to Zemplar. The severity of the aortic (thoracic, cardiac, abdominal regions) stomach and renal mineralization is greater in the Hospira paracalcitol treated groups at the same dose. This suggests a delay in the appearance and exacerbation of the mineralization with Hospira paracalcitol. The finding appears in males more than females likely because of the greater drug exposure in male.

*2 males had irregular adventitia

| **Histopathology Incidence 4-Week Rat** | **Control Hospira Paricalcitol** | | **Hospira Paricalcitol 10 µg/kg/day** | | **Abbott Paricalcitol (Zemplar) 10 µg/kg/day** | |
|---|---|---|---|---|---|---|
| | **M** | **F** | **M** | **F** | **M** | **F** |
| **Aorta mineralization, thoracic** | | | | | | |
| Main Study | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 min-mod | 0/10 |
| 2- Week Recovery | 0/5 | 0/5 | 2/5* severe | 0/5 | 3/5 min-mild | 0/5 |
| Total | 0 | 0 | 13% | 0 | 33% | 0 |
| **Aorta mineralization, heart** | | | | | | |
| Main Study | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 mild-mod | 0/10 |
| 2-Week Recovery | 0/5 | 0/5 | 3/5 min-severe | 0/5 | 4/5 minimal-moderate | 0/5 |
| Total | 0 | 0 | 20% | 0 | 40% | 0 |
| **Aorta mineralization, abdominal** | | | | | | |
| Main Study | 0/10 | 0/10 | 1/10 mild | 0/10 | 3/10 min-mod | 0/10 |
| 2-Week Recovery | 0/5 | 0/5 | 3/5 mild-severe | 0/5 | 3/5 severe | 0/5 |
| Total | 0 | 0 | 27% | 0 | 40% | 0 |
| **Stomach, mineralization, multifocal** | | | | | | |
| Main Study | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 min | 0/10 |
| 2-Week Recovery | 0/5 | 0/5 | 2/5 * * min-severe | 0/5 | 1/5 minimal | 0/5 |
| Total | 0 | 0 | 13% | 0 | 20% | 0 |
| **Renal mineralization** | | | | | | |
| Main Study | 0/10 | 0/10 | 3/10 minimal | 0/10 | 5/10 minimal | 0/10 |
| 2-week Recovery | 0/5 | 0/5 | 3/5 minimal | 0/5 | 2/5 minimal | 0/5 |
| Total | 0 | 0 | 40% | 0 | 47% | 0 |
| **Mammary Gland** | | | | | | |
| Main Study | 0/10 | 0/10 | 0/10 | 0/10 | 3/10 min | 0/10 |
| 2-week Recovery | 0/10 | 0/10 | 1/5 min | 0/10 | 1/5 min | 0/10 |
| Total | 0 | 0 | 7% | 0 | 27% | 0 |

**2 males had thickening of stomach wall



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**Table 2. Mean Toxicokinetic Data of Paricalcitol Hospira and Zemplar® from Rats Dosed 4 Weeks**

| Day | Dose (µg/kg/dose) | Sex | $AUC_{0-t}$ (h•ng/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | CLss/F (mL/h/kg) |
|---|---|---|---|---|---|---|
| 1 | Hospira 1.5 | Male | 32.35 | 8.05 | 0.50 | 46.37 |
| | | Female | 14.32 | 5.00 | 0.50 | 104.72 |
| | Hospira 10 | Male | 278.22 | 68.84 | 0.50 | 35.94 |
| | | Female | 157.98 | 52.05 | 0.50 | 63.30 |
| | Zemplar® 1.5 | Male | 30.63 | 7.90 | 0.50 | 48.98 |
| | | Female | 15.08 | 5.31 | 0.50 | 99.49 |
| | Zemplar® 10 | Male | 273.72 | 70.14 | 0.50 | 36.53 |
| | | Female | 171.56 | 56.50 | 0.50 | 58.29 |
| 26 | Hospira 1.5 | Male | 32.06 | 8.95 | 0.50 | 46.79 |
| | | Female | 15.07 | 4.94 | 0.50 | 99.54 |
| | Hospira 10 | Male | 250.30 | 60.23 | 0.50 | 39.95 |
| | | Female | 146.90 | 52.26 | 0.50 | 68.07 |
| | Zemplar® 1.5 | Male | 32.20 | 6.92 | 0.50 | 46.58 |
| | | Female | 16.93 | 5.84 | 0.50 | 88.60 |
| | Zemplar® 10 | Male | 230.40 | 58.49 | 0.50 | 43.40 |
| | | Female | 164.37 | 63.73 | 0.50 | 60.84 |

**Product differences in soft tissue mineralization may relate to** (b) (4)

Slight to moderate, occasionally statistically significant dose related increases in serum calcium were noted in 1.5 & 10 mcg/kg/day Hospira paracalcitol treatment groups for days 5, 12, 19 & 27 according to the sponsor. Paracalcitol decreases iPTH, resulting in the observed increases serum calcium. Elevated serum calcium is thought to correlate with tissue mineralization.

Treatment on Day 1 shows a statistically significant decrease (~4%) in serum calcium in males given 10 mcg/kg/day Hospira paracalcitol, but not in females and not with Zemplar. This initial, transient decrease in serum calcium can be attributed to the bolus infusion of the higher (b) (4) containing formulation in the Hospira treatment groups. In rats (b) (4) leads to hypocalcemia which increases iPTH however the increase in iPTH does not correct for the hypocalcemia (Shah JH, et al.;Metabolism 27(3) March 1978:257-260). This is in contrast with human experience where percutaneous injection of (b) (4) to the parathyroid is used to decrease iPTH release to treat hyperparathyroidism ( Douthat WG, et al; Int J Nephrol. 2011; 2011: 246734).

| Dose (µg/kg/dose) | | 0 (Control HS) | | 0 (Control ZM) | | 1.5 (Hospira Low) | | 10 (Hospira High) | | 1.5 (Zemplar® Low) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Animals | Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 0 | F: 10<br>F: 0 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 0 | F: 10<br>F: 0 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| **Pharmacodynamics (PD)** | | | | | | | | | | | | | |
| iPTH (pg/mL)[b] | Day 1 | 311.6 | 193.9 | 122.5 | 132.3 | 706.0 | 116.0 | 214.5 | 171.3 | 318.0 | 97.3 | 170.2 | 93.5 |
| | Day 5 | 315.7 | 126.1 | 387.5 | 150.3 | 210.2 | 82.6 | 53.8 | 65.5 | 844.0 | 86.2 | 57.7 | 65.5 |
| | Day 12 | 213.3 | 77.5 | 506.6 | 135.7 | 360.7 | 96.4 | 57.7 | 118.7 | 791.4 | 77.0 | 57.7 | 65.5 |
| | Day 19 | 423.7 | 53.8 | 222.9 | 85.0 | 84.4 | 57.7 | 57.7 | 65.5 | 120.4 | 69.1 | 57.7 | 65.5 |
| | Day 27 | 598.8 | 69.4 | 153.2 | 145.4 | 49.8 | 49.8 | 65.5 | 57.7 | 57.7 | 73.9 | 57.7 | 65.5 |
| Serum Phosphorus (mmol/L) | | - | - | - | - | - | - | - | - | - | - | - | - |
| Serum Calcium (mmol/L) | | | | | | | | | | | | | |
| | Day 1 | 2.79 | 2.70 | 2.69 | 2.74 | 2.73 | 2.82 | 2.65* | 2.80 | 2.64 | 2.70 | 2.75 | 2.75 |
| | Day 5 | 2.75 | 2.73 | 2.74 | 2.69 | 2.69 | 2.94* | 2.87 | 2.99* | 2.79 | 2.80 | 3.02* | 2.99* |
| | Day 12 | 2.75 | 2.81 | 2.70 | 2.78 | 2.82 | 3.01** | 3.04 | 3.01** | 2.85 | 2.89 | 3.25** | 2.99 |
| | Day 19 | 2.82 | 2.77 | 2.70 | 2.73 | 2.82 | 3.02 | 3.10* | 2.95 | 2.86 | 2.93* | 3.03** | 3.02** |
| | Day 27 | 2.81 | 2.77 | 2.75 | 2.71 | 3.21* | 3.02* | 3.72*** | 3.35*** | 3.26* | 3.08* | 3.67** | 3.27** |

* p<0.05 ** p<0.01 *** p<0.001

[redacted] (b) (4) metabolism is faster in female than male rodents and is associated with an increased elimination in females. This gender difference in [redacted] (b) (4) metabolism in rats may explain why the initial transient increase in serum calcium is seen in male but not female rats. [redacted] (b) (4) is metabolized by zero order kinetics i.e. a constant amount over time. [redacted] (b) (4) is a toxic hepatic metabolite of [redacted] (b) (4) formed from the rate limiting alcohol [redacted] (b) (4) reaches systemic circulation when the liver enzyme that metabolizes it to acetic acid reaches saturation. It is possible that the circulating [redacted] (b) (4) inhibits mitochondrial reactions and if one of these [redacted] (b) (4) sensitive reactions is CYP24 there may be impaired paracalcitol metabolism albeit a transient inhibition. Paracalcitol is metabolized through mitochondrial CYP24 (CYP24A1=24-hydroxylase that degrades vitamin D) and CYP3A4 and UGT1A4 enzymes. Part of the reason for the observed delay in soft-tissue mineralization may be the [redacted] (b) (4) (particularly at the 40% concentration) interfering with paracalcitol metabolism immediately following bolus injection. The exposure of paracalcitol is lower in females than males (41% lower with Hospira paracalcitol and 29% lower with Zemplar paracalcitol based on AUC). There is a corresponding increase in paracalcitol clearance in females compared to male rats. This relatively higher paracalcitol exposure in males may explain the increased tissue mineralization seen in Hospira treated males over females. There's a trend of increased clearance of Hospira paracalcitol relative to Abbott's Zemplar in female rats and a corresponding decrease in Cmax, AUC with the Hospira versus Abbott paracalcitol product in female rats.

## Clinical Risk Assessment

The initially observed differences in injection site histopathology discussed in the primary Pharmacology/Toxicology review do not appear to show a dose or formulation related trend. These injection site findings in rats if product related, might have greater clinical significance in dialysis patients as thrombus formation and tissue inflammation if exacerbated might impact the patency of the AV fistula for use with dialysis in patients with CKD and would be a cause for concern. However thrombus formation and inflammation observed at the injection site in rats does not show a clear drug or [redacted] (b) (4) related effect and appears to be



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sporadic observations of a variable nature.

A Tcon was held with DMEP and Hospira 10/13/11 to obtain clarification on how the paracalcitol would be administered during dialysis. Hospira indicated that the paracalcitol is administered into a port in the dialysis tubing which would dilute the 40% (b) (4) in the drug product down to ≤5% within 1-2 seconds of administration. Therefore the AV fistula would not receive direct administration of the 40% (b) (4) This is considered the same method used for administration of Abbott's Zemplar to dialysis patients; however the amount of (b) (4) exposure with the approved product Zemplar would be much lower than 5%.

Since the soft tissue mineralization is considered a function of hypercalcemia and CKD/dialysis patients have carefully controlled plasma calcium levels, the liability of tissue mineralization should be adequately controlled during clinical use. Therefore the apparent delay in soft-tissue mineralization seen with Hospira's paracalcitol compared to Abbott's Zemplar may relate to the higher (b) (4) concentration in the new Hospira formulation but may not achieve clinical significance. It does however indicate an observed difference between the products. This difference does not appear to have significant clinical relevance as monitoring serum calcium in the dialysis patient is part of the standard of care. While the appearance of the mineralization may differ between the products, the relatively lower overall incidence of soft-tissue mineralization suggests a potential advantage of Hospira's paracalcitol in treated male rats.

Findings from a one-month repeat dose toxicity study with a 2-week recovery in rats suggests a difference in toxicity profiles between Hospira's paracalcitol product and the listed drug Zemplar (paracalcitol). This difference in toxicity was observed as a time delay in the appearance of soft tissue mineralization in the aorta (thoracic, heart and abdominal regions) as well as the stomach and kidney as well as an increase in the severity scores for this finding in Hospira paracalcitol treated male rats compared to Zemplar. The absence of this observation in Hospira treated female rats may relate to differences in metabolism of (b) (4) and lower paracalcitol exposure in female rats. However this difference is qualitative and may reflect variability of the assay. It is noteworthy that there is an absence of any new toxicity findings between products based on this comparative rat toxicology study. Based on extensive experience with vitamin D analogues, serum calcium is generally considered an adequate biomarker for tissue mineralization. Therefore the observed qualitative differences between these paracalcitol products are unlikely to achieve clinical significance based on the routine monitoring of serum calcium in dialysis patients.

**Recommendations:**
Qualitative differences between the Hospira and Abbott paracalcitol products were observed in the appearance and severity of soft-tissue mineralization as outlined in the primary Pharmacology/Toxicology review. The one-month rat comparative toxicity study submitted in support of NDA 201-657, identified these



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differences. Since mineralization is attributed to hypercalcemia and serum calcium is routinely monitored in dialysis patients as part of the standard of care, it is unlikely that these differences observed in the comparative rat toxicity study would achieve a meaningful difference in clinical use or therapeutic outcome.

The primary reviewer recommends additional nonclinical studies to explore the effect of 40% (b) (4) on tissue mineralization and injection site inflammation over an extended recovery time as well as studies in a rat A-V fistula to address the potential clinical relevance of the prior observations. While these studies can be performed to explore possible mechanisms involved, they are not considered necessary as the difference between the products has been identified and characterized in the data submitted.

Based on the analysis described in this memo, Pharmacology/Toxicology recommends approval of NDA 201-657. The product label should reflect the 505b(2) nature of this application referencing the listed drug Zemplar for the appropriate Pharmacology/Toxicology sections (i.e. 8, 13) of the product label.



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/s/

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KAREN L DAVIS BRUNO
12/12/2011
Supervisory memo

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

| | |
|---|---|
| APPLICATION NUMBER: | 201657 |
| SUPPORTING NUMBER: | 3 |
| APPLICATION LETTER DATE: | 04/07/2011 |
| PRODUCT: | Paricalcitol Injection, 2 and 5µg/mL |
| INTENDED CLINICAL POPULATION: | Prevention and treatment of secondary hyperparathyroidism associated with CKD Stage 5 |
| SPONSOR: | Hospira INC |
| DOCUMENTS REVIEWED: | e-CTD submission. |
| REVIEW DIVISION: | DMEP |
| PHARM/TOX REVIEWER: | Parvaneh Espandiari. Ph.D |
| PHARM/TOX SUPERVISOR: | Karen Davis Bruno. Ph.D |
| DIVISION DIRECTOR: | Dr. Mary Parks |
| PROJECT MANAGER: | Jairath, Meghna |

Date of review submission to DARRTS: October 13, 2011



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## Executive Summary

### I. Recommendations

#### A. Recommendation on approvability:

Findings from the submitted nonclinical study suggested differences in the toxicity profiles between Hospira paricalcitol (HP) vs. RLD (Zemplar). Therefore, P/T recommends additional nonclinical studies to support the safety of the new HP formulation for marketing approval.

However, it is not clear how the new HP formulation will be administrated to patients during dialysis. If the HP infuses into the port of dialysis system, then the new HP formulation with a higher concentration of (b) (4) will be diluted. In this case, there will be less concerns about the safety of the new HP formulation and patients should be monitored for serum calcium levels as well as inflammation at the infusion site.

**Recommendation for nonclinical studies:**

Findings from a 4–week repeat dose toxicity study with a two week recovery in rats suggested: the delay in soft tissues mineralization at the aorta (thoracic, heart and abdominal), stomach; and increased inflammation at the infusion site (chronic vessel wall) in the HP-treated males. Therefore, additional nonclinical studies are required to assess the potential of a higher concentration of (b) (4) (40%) in the new HP formulation on tissue mineralization over the longer recovery time and elevated chronic vessel wall inflammation. These studies can be designed in the rat AV fistula model to address the effects of (b) (4) on chronic inflammation of the vessel walls (1 month with 2 week recovery with n=10); and a repeat dose toxicity studies (3 month with one month recovery with n=10) for soft tissues mineralization.

#### B. Recommendations on labeling:

**Section 8.1 Pregnancy**

Same as the RLD (Zemplar)

**Section 8.3 Nursing Mothers**

Same as the RLD (Zemplar)

.

**Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Same as the RLD (Zemplar)



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## II. Summary of nonclinical findings:

The new product, Hospira Paricalcitol (HP), has the same active ingredient, indications, route of administration and dosage form as the RLD, Zemplar®. A 4-week repeat dose intravenous study with a 2-week recovery period was conducted in rats as a bridging toxicity study to evaluate potential safety issues for the difference in the ratio of inactive ingredients in the RLD (20% (b) (4) and 30% propylene glycol) to the HP (40% (b) (4) and 10% propylene glycol).

Findings of this study presented pharmacological changes in both compounds (dose-related decreases in iPTH with slight to moderate increases in serum calcium levels) with increases in the relative weights of the kidneys to body weight in all HD treated animals and/or the relative weights of the adrenals to body weight in the HP-treated animals at HD. These changes were correlated with renal mineralization as well as the renal tubular basophilia/ tubular dilation at HD groups with both compounds.

In males at HD groups, the mean body weight gains were lower (ss) in both the HP (8.5%) and the RLD (8.6%) compared to the control groups during the main study. In addition, there was higher paricalcitol exposure in males compared to females (male female ratios: 2.26). The higher paricalcitol exposure in males was correlated with higher incidences soft tissues mineralization in males treated with both compounds.

Findings of this study suggested the differences in toxicity profiles of these two compounds based on the delay in the onset of tissues mineralization and elevated inflammation at the infusion site in the HP-treated males. At the end of the recovery study (2 week) the incidences of soft tissues mineralization in both compounds were almost similar. See Table below for the histopathological findings of soft tissue mineralization.

| | Control Hospira Paricalcitol | | Hospira Paricalcitol HD | | Abbott Paricalcitol HD | |
|---|---|---|---|---|---|---|
| | M | F | M | F | M | F |
| Aorta mineralization, thoracic | | | | | | |
| Main Study | **0/10** | 0/10 | 0/10 | 0/10 | 2/10 | 0/10 |
| Recovery Study | **0/5** | 0/5 | 2/5* | 0/5 | 3/5 | 0/5 |
| Aorta mineralization, heart | | | | | | |
| Main Study | **0/10** | 0/10 | 0/10 | 0/10 | 2/10 | 0/10 |
| Recovery Study | **0/5** | 0/5 | 3/5 | 0/5 | 4/5 | 0/5 |
| Aorta mineralization, abdominal | | | | | | |
| Main Study | **0/10** | 0/10 | 1/10 | 0/10 | 3/10 | 0/10 |
| Recovery Study | **0/5** | 0/5 | 3/5 | 0/5 | 3/5 | 0/5 |
| Stomach, mineralization, multifocal | | | | | | |
| Main Study | **0/10** | 0/10 | 0/10 | 0/10 | 2/10 | 0/10 |
| Recovery Study | **0/5** | 0/5 | 2/5 * * | 0/5 | 1/5 | 0/5 |
| Renal mineralization | | | | | | |
| Main Study | **0/10** | 0/10 | 3/10 | 0/10 | 5/10 | 0/10 |
| Recovery Study | **0/5** | 0/5 | 3/5 | 0/5 | 2/5 | 0/5 |

*sponsor indicated these 2 males had irregular adventitia

* * sponsor indicated these 2 males had thickening of stomach wall



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The histopathological findings at the infusion site were submitted for endothelial hyperplasia, mural thrombus and inflammation chronic vessel wall. Findings of these data suggested a higher percentage of inflammation at the infusion site in the HP-treated males at HD compared to the RLD (60% vs. 10%). The inflammation at the infusion site in the HP-treated males was still present at the end of the recovery (HP: 20% vs. RLD: 0%). Moreover, the comparison between two vehicle controls during both the main and the recovery studies also showed higher incidences of inflammation at the infusion site with the HP vehicle compared to the Zemplar vehicle ( (b) (4) concentration 40% vs. 20%). See Tables below for the histopathological findings at the infusion site:

| Main Study (4 Weeks) | | | | | | |
|---|---|---|---|---|---|---|
| Groups | Endothelial Hyperplasia | | Mural Thrombus | | Inflammation Chronic Vessel Wall | |
| | **M** | **F** | **M** | **F** | **M** | **F** |
| HP Vehicle (40% (b) (4) | 5/10=50% | 7/10=70% | 7/10=70% | 2/10=20% | 3/10=30% | 4/10=40% |
| HP (LD) | 0/4=0% | 2/4=50% | 4/4=100% | 3/4=75% | 0/4=0% | 0/4=0% |
| HP (HD) | 5/10=50% | 4/10=40% | 5/10=50% | 6/10=60% | **6/10=60%** | 1/10=10% |
| Zemplar Vehicle (20% (b) (4) | 0/7=0% | 2/4=50% | 6/7=85% | 2/4=50% | 1/7=14% | 2/4=50% |
| Zemplar (LD) | 3/6=50% | 1/5=20% | 4/6=66% | 5/5=100% | 0/6=0% | 1/5=20% |
| Zemplar (HD) | 5/10=50% | 3/10=30% | 8/10=80% | 5/10=50% | 1/10=10% | 2/10=20% |

| Recovery Study (2 Weeks) | | | | | | |
|---|---|---|---|---|---|---|
| Groups | Endothelial Hyperplasia | | Mural Thrombus | | Chronic Inflammation Vessel Wall | |
| | M | F | M | F | M | F |
| HP Vehicle (40% (b) (4) | 0/5=0% | 1/5=20% | 1/5=20% | 2/5=40% | **1/5=20%** | 1/5=20% |
| HP (HD) | 2/5=40% | 1/5=20% | 2/5=40% | 0/5=0% | **1/5=20%** | 3/5=60% |
| Zemplar Vehicle (20% (b) (4) | 0/3=0% | 3/3=100% | 2/3=66% | 2/3=66% | 0/3=0% | 1/3=33% |
| Zemplar (HD) | 2/5=40% | 2/5=40% | 3/5=60% | 4/5=80% | 0/5=0% | 1/3=33% |

*Reviewer: The sponsor reported that the histopathological examination was performed on tissues from 3 groups of control Hospira, HD Hospira and HD Zemplar from the main and the recovery studies. However, in the submitted NDA, in the appendix 11, small numbers of animals were evaluated from LD and control Zemplar treated animals for the infusion site histopathology which were included in Tables above. In addition, there were differences in number of incidences in the sponsor summary tables with the sponsor result tables. Incidences in Tables above were selected from the result section of the NDA package.*

In Summary, findings of this study suggested differences in toxicity profiles between the HP and the RLD in following:

1. The delay in the onset of soft tissue mineralization (aorta: thoracic, heart; and stomach) was observed only in the HD treated males given the HP. Although at the end of the recovery study (2 week) these incidences were almost similar between two compounds, it is not known how the incidences of soft tissues mineralization would



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manifest over a longer recovery time. Given that, the soft tissues mineralization can be prevented by monitoring the serum calcium in subjects during the clinical studies.

2. The increased inflammation at the infusion site was reported at HD in males given the HP compared to the RLD. In this study, rats received i.v. infusion of ~0.8 mL of the HP compound (hold 0.3 ml of (b) (4) The MRHD will be 7 mcg or 1.4 mL of the HP formulation (hold ~0.6 ml (b) (4) Consequently, at the local site in humans, the (b) (4) concentration will be 2X more. Therefore, the increased inflammation at the infusion site is an important safety concern and clinically relevant especially for patients with the AV fistulas.

However, in the submitted NDA, it is not clear how the new HP formulation will be used during dialysis. If the HP compound dilutes before administration (for example by infusing inside of the port of dialysis), in that case, there will be less concern about inflammation at the infusion site. The margin of safety for the systemic (b) (4) concentration in human compared to rats will be more than 100 fold.

**A. Pharmacologic activities**:

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring. Paricalcitol's biological actions are mediated through binding to the Vitamin D receptor (VDR), which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

**B. Pharmacokinetics activity:**

Concentration of paricalcitol injection (i.v.) decreased rapidly within 2 hrs after administration (range of 0.04 to 0.24 mcg/kg); then, the concentrations of paricalcitol declined log-linearly. No accumulation of paricalcitol was observed with multiple dosing.

**C. Nonclinical safety issues relevant to clinical use:**

Two safety issues were established relevant to the clinical use as following: the delay in the onset of soft tissue mineralization (aorta: thoracic, heart; and stomach); and inflammation at the infusion site (see above for more details).



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## *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 201657

**Review number**: 1

**Supporting document#/date/type of submission**: 3/April 07, 2011/ 505(b)(2)

**Information to sponsor**: Yes (X) No ()

**Sponsor and/or agent**: Hospira INC

**Manufacturer for drug substance**: Formosa Laboratories, Inc.

**Reviewer name:** Parvaneh Espandiari

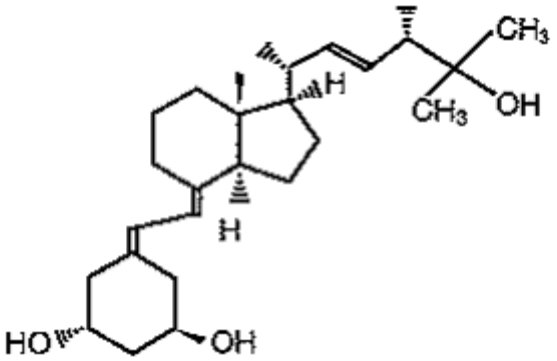
**Division name**: DMEP

**HFD #**: 510

**Review completion date**: September 23, 2011

**Drug**:

**Trade name:** (1α,3β,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol
**CAS registry number:** 131918-61
**Molecular formula/molecular weight:** C27H44O3/416.64 AMU
**Structure:**




**Relevant INDs/NDAs/DMFs**: NDA 020819

**Drug class**: Vitamin D analogue of calcitriol



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**Intended clinical population**: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.

**Clinical formulation**:
See Table below from the sponsor:

| Component | Hospira Quantity per Milliliter (mL) | Innovator Quantity per Milliliter (mL) | Function | Reference to Standards |
|---|---|---|---|---|
| Paricalcitol | 2 mcg<br>Or<br>5 mcg | 2 mcg<br>Or<br>5 mcg | Active ingredient | USP |
| Alcohol (Ethanol, USP, 190-Proof) Non-Beverage | 340 mg | 170 mg | Cosolvent | USP |
| Propylene Glycol | 100 mg | 300 mg | Cosolvent | USP |
| Water for Injection | q.s. to 1.00 mL | q.s. to 1.00 mL | Vehicle | USP/Ph Eur |
| Total Volume | 1.00 mL | 1.00 mL | | |
| q.s. = Quantity sufficient | | | | |

No excipients exceed the IIG limits for maximum daily dose and route of administration. Dosage forms and strengths are: Paricalcitol injection as a multi-use vial for 2 mcg/1 mL, 5 mcg/1 mL and 10 mcg/2 mL. In 2 or 5 ug/mL solution for injection, the concentrations of (b) (4) and propylene glycol are 20%v/v and 30% v/v (respectively) in RLD and 40% v/v and 10% v/v (respectively) in Hospira Paricalcitol.

**Route of administration**:
Intravenous

**Disclaimer**: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Data reliance**: Except as specifically identified below, all data and information discussed below necessary for approval of NDA201657 are owned by Hospira Inc. or are data for which Hospira Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 201657 that Hospira Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Hospira Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA201657.

**Studies reviewed within this submission:**
A 4-week repeat dose toxicity studies in rats

**Studies not reviewed within this submission**:
None



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## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

No new information.

### 2.6.2.2 Primary pharmacodynamics

No new information.

### 2.6.2.3 Secondary pharmacodynamics

No new information.

### 2.6.2.4 Safety pharmacology

No new information.

### Pharmacodynamic drug interactions

No new information.

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

No new information.

## 2.6.6 TOXICOLOGY

### 2.6.6.1 Overall toxicology summary

Summary:

A 4-week repeat dose toxicity study in Sprague Dawley rats with a 2-week recovery period was conducted to assess the potential toxicity as well as to compare TK and PD of the HP to the RLD. Findings of this study showed consistency between the pharmacological effects of the new product to the RLD. New toxicity profiles were identified as following: the delay in the onset of the mineralization of soft tissues, and increased inflammation at the infusion site in the HP-treated males at HD compared to the RLD.

**Study title:**

**A 4-week repeat dose intravenous toxicity study with a 2-week recovery period in rats**

Key findings:

- In males, at HD groups, the mean body weight gains (ss) were lower in the HP (8.5%) and the RLD (8.6%) compared to the control groups during the main study. At the end of the study, the mean body weight gains were comparable in all groups. In addition, there was higher paricalcitol exposure in males compared to females (male female ratios: 2.26), which correlated to higher incidences of soft tissue mineralization in males.
- Different doses of both compounds induced a similar extent of pharmacological effects (dose-response decreased iPTH levels and increased serum calcium levels). In addition, the relative weights of the kidneys increased to body weight at HD groups (HP: 8.3% M; 13.3% F and RLD: 9.8%M; 11.6% F) and/or adrenal relative weights to the body weights increased only at HD treated with the HP (41.8%M; 20.4%F). At the end of the study, organ weights were comparable in all animals.



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- At HD groups, increased incidences of soft tissues mineralization in the different regions of the aorta and the stomach were reported for: the RLD males during both the main and the recovery studies; and for the HP males only during the recovery study suggesting delayed effect in soft tissues mineralization with the new HP formulation. At the end of the recovery study, incidences of soft tissues mineralization were similar between two compounds.
- In males at HD, at the infusion site, higher incidences of inflammation were reported in the HP-treated animals compared to the RLD (60% vs. 10%). At the end of the study, inflammation at the infusion site was still presented only in the HP-treated animals (in males: HP 20% vs. 0% RLD; in females: 60% vs. 33%).

**Study no.**: 71332
**Conducting laboratory and location**: ITR Laboratories Canada Inc (ITR)
**Date of study initiation**: November 22, 2010
**GLP compliance**: yes
**QA report**: yes (X) no ( )
**Drug, lot #, and % purity**: Paricalcitol, H0I227; and %100.0
**Control HS:** Control HS: Hospira Placebo (Propylene Glycol: (b) (4) Water; 10:40:50 v/v/v); Lot #: NB 02442:064; manufacturer: Hospira, Inc.
**Control ZM:** Zemplar Placebo: (Propylene Glycol: (b) (4) Water; 30:20:50 v/v/v); Lot #: NB 02442:065; manufacturer: Hospira, Inc.

**Methods**

<table>
<tr><td>Doses:</td><td>Total of 12 doses for controls and test articles in both female and male animals as following: 0, 1.5 and 10ug/kg/day Hospira and 0, 1.5 and 10ug/kg/day Zemplar. Dosing on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26. See Table below from the sponsor:
<table>
<tr><th rowspan="3">Group No.</th><th rowspan="3">Group Designation</th><th rowspan="3">Dose Level (µg/kg/dose)</th><th rowspan="3">Dose Conc (µg/mL)</th><th rowspan="3">Dose Volume (mL/kg)</th><th colspan="4">Toxicology Animals</th><th colspan="2" rowspan="2">TK Animals</th><th colspan="2" rowspan="2">PD Animals***</th></tr>
<tr><th colspan="2">Main</th><th colspan="2">Recovery</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>1*</td><td>Control HS</td><td>0</td><td>0</td><td>2</td><td>10</td><td>10</td><td>5</td><td>5</td><td>3</td><td>-</td><td>6</td><td>6</td></tr>
<tr><td>2**</td><td>Control ZM</td><td>0</td><td>0</td><td>2</td><td>10</td><td>10</td><td>5</td><td>5</td><td>3</td><td>-</td><td>6</td><td>6</td></tr>
<tr><td>3</td><td>Hospira Low</td><td>1.5</td><td>5.0</td><td>0.3</td><td>10</td><td>10</td><td>-</td><td>-</td><td>6</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>4</td><td>Hospira High</td><td>10</td><td>5.0</td><td>2</td><td>10</td><td>10</td><td>5</td><td>5</td><td>6</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>5</td><td>Zemplar® Low</td><td>1.5</td><td>5.0</td><td>0.3</td><td>10</td><td>10</td><td>-</td><td>-</td><td>6</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>6</td><td>Zemplar® High</td><td>10</td><td>5.0</td><td>2</td><td>10</td><td>10</td><td>5</td><td>5</td><td>6</td><td>6</td><td>6</td><td>6</td></tr>
</table>
M = Male; F = Female; Conc = Concentration; PD = Pharmacodynamic<br>
* The Control HS animals from Group 1 received the **Hospira Placebo** (alone) used in the preparation of the dose formulations of Groups 3 and 4.<br>
** The Control ZM animals from Group 2 received the **Zemplar Placebo** (alone) used in the preparation of the dose formulations of Groups 5 and 6.<br>
*** A subset of 3 animal/sex/group had iPTH analysis and the second subset of 3 animal/sex/group had Calcium (Ca) & Phosphorus (Phos) analyses.</td></tr>
<tr><td>Species/source</td><td>Sprague Dawley/ Charles River, Canada Inc.,</td></tr>
<tr><td>Age:</td><td>10 weeks old</td></tr>
<tr><td>Weight:</td><td>307 g to 464 g for males and from 202 g to288 g for females.</td></tr>
<tr><td>Number/sex/group: (main study)</td><td>10/sex/group (6 dose groups)</td></tr>
<tr><td>Number/sex/group (TK)</td><td>6/sex/group (Hospira LD, Hospira HD, Zemplar LD and Zemplar HD; and 3/group for male Control Hospira Placebo and Zemplar placebo)</td></tr>
</table>



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| | |
|---|---|
| Number/sex/group (recovery) | 5/sex/group for: Controls (Hospira placebo and Zemplar placebo); and HD groups (Zemplar and Hospira) |
| Route, formulation, dose volume | For treatment, the intravenous catheter inserted into the femoral vein and advanced into the *vena cava*. The catheter was exteriorized at the nape of the neck using a metal stylet which created a subcutaneous tunnel from the inguinal area to the dorso-cervical area. The infusion rate was controlled by an infusion pump. Rats were administered paracalcitol by bolus IV injection to the indwelling catheter. Dosing: 3X/week, for 4 weeks (total of 12 doses on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26). Formulation for HP: 5 µg/mL solution in placebo (aqueous 10% (v/v) propylene glycol, 40% (v/v) alcohol ( (b) (4) and 50% (v/v) water; 2 mL/kg for the animals of Groups 1, 2, 4 and 6, and 0.3 mL/kg for the animals of Groups 3 and 5, respectively. |

**Study Design Summary:**

**Observation and Times:**

| | |
|---|---|
| Clinical Findings: | recorded daily |
| Body weights: | recorded on the day of arrival, first day of study and weekly during the treatment as well as terminally prior to |
| Food consumption: | Weekly: pre-treatment period, throughout treatment and recovery periods |
| Ophthalmoscopy: | performed before treatment, once at the end of the treatment period |
| Urinalysis: | Urine samples on Day 28 (Main study) and on Day 42 (Recovery study) |
| Hematology and Clinical Chemistry: | Blood samples on Day 28 (Main study) and on Day 42 (Recovery study) |
| Gross pathology: | For specified organs/tissues |
| Organ weights: | specified organs/tissues were weighed at termination |
| Toxicokinetics: | 6 blood samples (0.5 mL each) were collected on Days 1 and 26 at pre-dose, 0.5, 2, 6, 12 and 24 hours after treatment (3 rats/sex/group/time point). 2 cohorts from groups 3 to 6 (except for the Control animals; 3 male rats/group). |
| Histopathology: | Specified organs/tissues were fixed (4%formaldehyde) and examined.<br>*Reviewer: The sponsor reported that the histopathological examination was performed on tissues from 3 groups of control Hospira, HD Hospira and HD Zemplar from the main and the recovery studies. However, in the submitted NDA, in the appendix 11, small numbers of animals were evaluated from LD and control Zemplar treated animals for the infusion site histopathology which were included in Tables in Page 5.*<br>Adequate Battery: yes (X), no ( )<br>Peer review: yes (X), no ( )<br>See the Table below from sponsor for tissues that were inspected: |



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| ORGANS/TISSUES | Retain (•) | Weigh (√) | Examine (€) |
|---|---|---|---|
| Adrenals | • | √ | € |
| Animal identification | • | | |
| Aorta (thoracic) | • | | € |
| Blood | • | | |
| Bone marrow smears (3) | • | | |
| Brain | • | √ | € |
| Cecum | • | | € |
| Colon | • | | € |
| Epididymides | •d | | € |
| Esophagus | • | | € |
| Eyes | •a | | € |
| Femur & marrow | • | | € |
| Heart | • | √ | € |
| Kidneys | • | √ | € |
| Liver (2 lobes) | • | √ | € |
| Lungs (2 lobes) | •bc | √ | € |
| LN, mandibular | • | | € |
| LN, mesenteric | • | | € |
| Mammary gland (inguinal) | • | | € |
| Optic nerves | •a | | € |
| Ovaries | • | √ | € |
| Pancreas | • | | € |
| Pituitary | • | √ | € |
| Prostate | • | √ | € |
| Rectum | • | | € |
| SG, mandibular | • | | € |
| Sciatic nerve | • | | € |
| Seminal vesicles | • | | € |
| Skeletal muscle | • | | € |
| Skin & subcutis (inguinal) | • | | € |

| ORGANS/TISSUES | Retain (•) | Weigh (√) | Examine (€) |
|---|---|---|---|
| Duodenum | • | | € |
| Jejunum | • | | € |
| Ileum | • | | € |
| SC, cervical | • | | € |
| Spleen | • | √ | € |
| Sternum & marrow | • | | € |
| Stomach | • | | € |
| Testes | •d | √ | € |
| Thymus | • | √ | € |
| Thyroid gland/parathyroids | • | √ | € |
| Tongue | • | | € |
| Trachea | •c | | € |
| Urinary bladder | • | | € |
| Uterus | • | √ | € |
| Vagina | • | | € |
| | | | |
| Abnormal findings | • | | € |
| | | | |
| | | | |
| **Additional Tissues presented below** | | | |
| Infusion site (vena cava) | • | | € |

| | |
|---|---|
| a | Davidson's fluid |
| b | Lungs were infused with 10% neutral buffered formalin |
| c | Lungs were weighed with trachea and recorded in Provantis as lungs in organ weight record |
| d | Bouin's fluid |
| | |
| LN | Lymph node |
| SG | Salivary gland |
| SC | Spinal cord |
| € | Examine microscopically |

**Notes:**
Paired organs weighed together
Parathyroids, mammary gland and optic nerves were examined histologically, only if present in routine sections

| **Hematology** [a] | | |
|---|---|---|
| **Parameter** | **Examined** | **Not examined** |
| Hemoglobin (HGB) | x | |
| Hematocrit (HCT) | x | |
| Red blood cell count (RBC) | x | |
| Reticulocyte count | x | |
| Platelet count (PLT) | x | |
| Mean platelet volume (MPV) | | x |
| Mean corpuscular volume (MCV) | x | |
| Mean corpuscular hemoglobin (MCH) | x | |
| Mean corpuscular hemoglobin concentration (MCHC) | x | |
| Red cell distribution width (RDW) | | x |
| Hemoglobin distribution width (HDW) | | x |
| White Blood cell count (WBC) | x | |

| | | |
|---|---|---|
| Differential leukocyte count (% and absolute) | | x |
| Cytologic morphology | | x |
| Platelet morphology | | x |
| Leukocyte morphology | | x |
| Activated Partial Thromboplastin Time (APTT) | | x |
| Prothrombin Time (PT) | | x |

[a] Observations/Times: main animals on Day 28 and recovery animals on Day 42

| **Clinical Chemistry [a]** | | |
|---|---|---|
| **Parameter** | **Examined** | **Not examined** |
| Aspartate aminotransferase (AST) | x | |
| Alanine aminotransferase (ALT) | x | |
| Alkaline phosphatase (ALP) | x | |
| Blood urea nitrogen (BUN) | x | |
| Creatinine | x | |
| Glucose | x | |
| Cholesterol | x | |
| Triglycerides | x | |
| Total protein | x | |
| Albumin | x | |
| Globulin | x | |
| Albumin/globulin | x | |
| Total bilirubin | x | |
| Sodium | x | |
| Potassium | x | |
| Chloride | x | |
| Calcium | x | |
| Phosphorous ($PO_4$) | x | |
| Gamma-glutamyl transferase (GGT) | | x |

[a] Observations/Times: main animals on Day 28 and recovery animals on Day 42

**Parameters that were tested in urine:** See Table below from the sponsor:

Bilirubin
Blood
Color and appearance
Glucose
Ketones
pH
Protein
Sediment microscopy
Specific gravity
Urobilinogen
Volume



Reference ID: 3028604

**Results:**

There were no reports of any mortality or changes in clinical signs, food consumption, ocular, hematology, coagulation, and urinalysis.

Body weights:

At HD in all males, the mean body weight gains were lower (ss) in both the HP (8.5%) and the RLD (8.6%) compared to the control groups. However, the body weight gains were increased greater in males at HD groups during the recovery period compared to females at HD groups. See Tables below from the sponsor:

Main study:

| Group No. | Group Designation |
|---|---|
| 1 | Control HS |
| 3 | Hospira Low |
| 4 | Hospira High |

| Group No. | Group Designation |
|---|---|
| 2 | Control ZM |
| 5 | Zemplar® Low |
| 6 | Zemplar® High |

| Group Identification (Dose Level) | Body Weight Gain (%) | | | |
|---|---|---|---|---|
| | Males | | Females | |
| | Days -1 to 27 | Days 27 to 41 | Days -1 to 27 | Days 27 to 41 |
| Group 1 (0 µg/kg/dose) | +31.5 | +10.9 | +22.8 | +7.9 |
| Group 3 (1.5 µg/kg/dose) | +32.1 | NA | +23.1 | NA |
| Group 4 (10 µg/kg/dose) | **+23.0*** | +23.7 | +19.8 | +11.4 |

* p< 0.05 NA not applicable

| Group Identification (Dose Level) | Body Weight Gain (%) | | | |
|---|---|---|---|---|
| | Males | | Females | |
| | Days -1 to 27 | Days 27 to 41 | Days -1 to 27 | Days 27 to 41 |
| Group 2 (0 µg/kg/dose) | +30.4 | +13.5 | +21.1 | +3.3 |
| Group 5 (1.5 µg/kg/dose) | +34.6 | NA | +24.3 | NA |
| Group 6 (10 µg/kg/dose) | **+21.8*** | +23.3 | +21.7 | +8.1 |

* p< 0.05 NA not applicable

Recovery study:

BEST AVAILABLE COPY

| Sex: Male | | Day(s) Relative to Start Date | |
|---|---|---|---|
| | | 34 | 41 |
| Group 1 | Mean | 541 [R1] | 579 [I2] |
| 0 | SD | 49.5 | 61.4 |
| µg/kg/dose | N | 5 | 5 |
| Group 4 | Mean | 567 | 621 |
| 10 | SD | 43.4 | 44.8 |
| µg/kg/dose | N | 5 | 5 |

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

[1][R - Automatic Transformation Selected: Rank]

[2][I - Automatic Transformation Selected: Identity (No Transformation)]

| Sex: Female | | Day(s) Relative to Start Date | |
|---|---|---|---|
| | | 34 | 41 |
| Group 1 | Mean | 299 [I1] | 314 [I1] |
| 0 | SD | 27.6 | 32.7 |
| µg/kg/dose | N | 5 | 5 |
| Group 4 | Mean | 315 | 323 |
| 10 | SD | 12.1 | 10.2 |
| µg/kg/dose | N | 5 | 5 |

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic

[1][I - Automatic Transformation Selected: Identity (No Transformation)]



Reference ID: 3028604

BEST AVAILABLE COPY

| Sex: Male | | Day(s) Relative to Start Date | |
|---|---|---|---|
| | | 34 | 41 |
| Group 2 | Mean | 553 [L1] | 589 [R2] |
| 0 | SD | 35.6 | 36.1 |
| µg/kg/dose | N | 5 | 5 |
| Group 6 | Mean | 545 | 592 |
| 10 | SD | 62.2 | 66.8 |
| µg/kg/dose | N | 5 | 5 |

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic
[1][L - Automatic Transformation Selected: Log]
[2][R - Automatic Transformation Selected: Rank]

| Sex: Female | | Day(s) Relative to Start Date | |
|---|---|---|---|
| | | 34 | 41 |
| Group 2 | Mean | 295 [I1] | 308 [R2] |
| 0 | SD | 12.4 | 7.3 |
| µg/kg/dose | N | 5 | 5 |
| Group 6 | Mean | 309 | 321 |
| 10 | SD | 17.4 | 22.4 |
| µg/kg/dose | N | 5 | 5 |

Statistical Test: Generalised Anova/Ancova Test Transformation: Automatic
[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]

Hematology:
No remarkable changes in any treatment groups.

Clinical chemistry:
Dose-related decreases in iPTH (maximally for both compounds on Day 19 for LD and on Day 5 for HD) as well as increases in serum calcium levels (peaked on Day 27 at LD and HD for both compounds) were reported. There was no clear difference in the severity of the changes between sexes.
See Tables below from the sponsor:

| Dose (µg/kg/dose) | | 0 (Control HS) | | 0 (Control ZM) | | 1.5 (Hospira Low) | | 10 (Hospira High) | | 1.5 (Zemplar® Low) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Animals | Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 0 | F: 10<br>F: 0 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 0 | F: 10<br>F: 0 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| **Pharmacodynamics (PD)** | | | | | | | | | | | | | |
| iPTH (pg/mL)[6] | Day 1 | 311.6 | 193.9 | 122.5 | 132.3 | 706.0 | 116.0 | 214.5 | 171.3 | 318.0 | 97.3 | 170.2 | 93.5 |
| | Day 5 | 315.7 | 126.1 | 387.5 | 150.3 | 210.2 | 82.6 | 53.8 | 65.5 | 844.0 | 86.2 | 57.7 | 65.5 |
| | Day 12 | 213.3 | 77.5 | 506.6 | 135.7 | 360.7 | 96.4 | 57.7 | 118.7 | 791.4 | 77.0 | 57.7 | 65.5 |
| | Day 19 | 423.7 | 53.8 | 222.9 | 85.0 | 84.4 | 57.7 | 57.7 | 65.5 | 120.4 | 69.1 | 57.7 | 65.5 |
| | Day 27 | 598.8 | 69.4 | 153.2 | 145.4 | 49.8 | 49.8 | 65.5 | 57.7 | 57.7 | 73.9 | 57.7 | 65.5 |
| Serum Phosphorus (mmol/L) | | - | - | - | - | - | - | - | - | - | - | - | - |
| Serum Calcium (mmol/L) | | | | | | | | | | | | | |
| | Day 1 | 2.79 | 2.70 | 2.69 | 2.74 | 2.73 | 2.82 | 2.65* | 2.80 | 2.64 | 2.70 | 2.75 | 2.75 |
| | Day 5 | 2.75 | 2.73 | 2.74 | 2.69 | 2.69 | 2.94* | 2.87 | 2.99* | 2.79 | 2.80 | 3.02* | 2.99* |
| | Day 12 | 2.75 | 2.81 | 2.70 | 2.78 | 2.82 | 3.01** | 3.04 | 3.01** | 2.85 | 2.89 | 3.25** | 2.99 |
| | Day 19 | 2.82 | 2.77 | 2.70 | 2.73 | 2.82 | 3.02 | 3.10* | 2.95 | 2.86 | 2.93* | 3.03** | 3.02** |
| | Day 27 | 2.81 | 2.77 | 2.75 | 2.71 | 3.21* | 3.02* | 3.72*** | 3.35*** | 3.26* | 3.08* | 3.67** | 3.27** |

* p<0.05 ** p<0.01 *** p<0.001

Hematology and Coagulation parameters:
No remarkable changes

Urinalysis:
Not remarkable changes

Organ weights:
Only the HP-treated animals were evaluated for any changes in organ weights as well as kidneys in Zemplar groups. In these organs, at HD, increases in kidneys and adrenals weights were noted as following:
Main study



Reference ID: 3028604

- Kidneys: increases in the mean absolute weight (HP: 2.3% M; 10.0% F; Zemplar: 3.8%M; 9.1%F) and relative body weight (HP: 8.3% M; 13.3%F; Zemplar: 9.8M; 11.6%F)
- Adrenals: in the HP treated animals, increases in the mean absolute weight (30.8% M; 16.9% F); and relative body weight (41.8% M; 20.4% F)

Recovery study

Organ weights were comparable to control animals.

See Tables below from the sponsor:

| Dose (µg/kg/dose) | 0 (Control HS) | | 0 (Control ZM) | | 1.5 (Hospira Low) | | 10 (Hospira High) | | 1.5 (Zemplar® Low) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Animals Main / Recovery | M: 10 M: 5 | F: 10 F: 5 | M: 10 M: 5 | F: 10 F: 5 | M: 10 M: 0 | F: 10 F: 0 | M: 10 M: 5 | F: 10 F: 5 | M: 10 M: 0 | F: 10 F: 0 | M: 10 M: 5 | F: 10 F: 5 |
| **Adrenal Weights at termination; Day 28** | | | | | | | | | | | | |
| Absolute (grams) | 0.0731 | 0.0723 | - | - | - | - | 0.0956** | 0.0845 | - | - | - | - |
| Percent difference from control | NA | NA | - | - | - | - | +30.8 | +16.9 | - | - | - | - |
| Body weight ratio (%) | 0.0146 | 0.0265 | - | - | - | - | 0.0207*** | 0.0319** | - | - | - | - |
| Percent difference from control | NA | NA | - | - | - | - | +41.8 | +20.4 | - | - | - | - |
| **Kidney Weights at termination; Day 28** | | | | | | | | | | | | |
| Absolute (grams) | 2.8971 | 1.6441 | 2.8997 | 1.6563 | - | - | 2.9627 | 1.8084* | - | - | 3.0100 | 1.8078 |
| Percent difference from control | NA | NA | NA | NA | - | - | +2.3 | +10.0 | - | - | +3.8 | +9.1 |
| Body weight ratio (%) | 0.5875 | 0.6044 | 0.5978 | 0.5841 | - | - | 0.6362 | 0.6845** | - | - | 0.6564** | 0.6517** |
| Percent difference from control | NA | NA | NA | NA | - | - | +8.3 | +13.3 | - | - | +9.8 | +11.6 |

Complete organ weights data in Appendix.

**Gross Pathology:**

Kidneys:

Main study

- Irregular surface/ mottling was reported in treated males: HP (1/control); Zemplar (2/LD and 4/HD)
- Pale discoloration/irregular surface was reported only in one male at HD given HP. See Table below from the sponsor:

| Sex | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | 0HS | 0ZM | 1.5H | 10H | 1.5Z | 10Z | 0HS | 0ZM | 1.5H | 10H | 1.5Z | 10Z |
| Number of animals examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Kidneys | | | | | | | | | | | | |
| Mottled/irregular surface | 1 | 0 | 0 | 0 | 2 | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale discoloration/irregular surface | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

HS = Control HS group; ZM = Control ZM group; H = Paricalcitol Hospira group; Z = Zemplar (Comparator) group

Recovery study:

Irregular surface/pale discoloration was still present in males at HD: 1 in Zemplar and 1 in HP. See Table below from the sponsor:



Reference ID: 3028604

| Sex | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | 0HS | 0ZM | 10H | 10Z | 0HS | 0ZM | 10H | 10Z |
| Number of animals examined | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Kidneys | | | | | | | | |
| Pale discoloration /irregular surface | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

Infusion Site:

Main study

Dark/pale material (with or without thickening of the vessel wall) was reported at the injection site in all treated animals. See Table below from the sponsor:

| Sex | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | 0HS | 0ZM | 1.5H | 10H | 1.5Z | 10Z | 0HS | 0ZM | 1.5H | 10H | 1.5Z | 10Z |
| Number of animals examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Infusion site | | | | | | | | | | | | |
| Dark/pale material/thickening | 7 | 7 | 4 | 7 | 6 | 10 | 3 | 4 | 4 | 7 | 5 | 8 |

HS = Control HS group; ZM = Control ZM group; H = Paricalcitol Hospira group; Z = Zemplar (Comparator) group

Recovery study

Pale or dark material (with or without thickening of the vessel wall) was still presented at HD treated animals: Zemplar (4 M; 2F); HP (5M; 2F) as well as in control animals: Zemplar (3M; 3F); HP: (1M; 2F). See Table below from the sponsor:

| Sex | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | 0HS | 0ZM | 10H | 10Z | 0HS | 0ZM | 10H | 10Z |
| Number of animals examined | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Infusion site | | | | | | | | |
| Dark/pale material/ Thickening | 1 | 3 | 5 | 4 | 2 | 3 | 2 | 2 |

HS = Control HS group; ZM = Control ZM group; H = Paricalcitol Hospira group; Z = Zemplar (Comparator) group

*Reviewer: this incidence might be due to the biological variations since there was lower in the control animals from the recovery study compared to control animals from the main study.*

Complete gross pathology data in the appendix.

Histopathology:

Adequate Battery: yes (x), no ( ) — explain

Peer review: yes (x), no ( )

Aorta at level of infusion site for heart, thoracic, abdominal:

Main study

Treatment-related mineralization was reported only in males at HD as following: Zemplar: thoracic (2); heart (2) and infusion site (3); HP: infusion site (1). See Table below from the sponsor:



Reference ID: 3028604

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **10** | **10** | **10** | **10** | **10** | **10** |
| **Tissue: Finding** | **Severity** | | | | | | |
| **Aorta (thoracic):** Mineralization | | **0** | **0** | **2** | **0** | **0** | **0** |
| | minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| **Aorta (heart):** Mineralization | | **0** | **0** | **2** | **0** | **0** | **0** |
| | mild | 0 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| **Aorta (abdominal)(infusion site):** Mineralization | | **0** | **1** | **3** | **0** | **0** | **0** |
| | minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| | mild | 0 | 1 | 0 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 2 | 0 | 0 | 0 |

Recovery study:
Mineralization was still present at the aorta site (heart, thoracic and abdominal) in HD treated males as following: heart: Zemplar (4) and HP (3); thoracic: Zemplar (3) and HP (2); infusion site Zemplar (3) and HP (3). Data from the recovery study suggested that HP-treated males had delayed onset of the mineralization in the aorta (heart and thoracic) compared to the Zemplar-treated males. In addition, mineralization of the thoracic in 2 males in the HP at HD was correlated with the irregular surface of the adventitia from the histopathology report. See Table below from the sponsor:

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **5** | **5** | **5** | **5** | **5** | **5** |
| **Tissue:** Finding | **Severity** | | | | | | |
| **Aorta (thoracic):** Mineralization | | **0** | **2** | **3** | **0** | **0** | **0** |
| | minimal | 0 | 0 | 2 | 0 | 0 | 0 |
| | mild | 0 | 0 | 1 | 0 | 0 | 0 |
| | severe | 0 | 2 | 0 | 0 | 0 | 0 |
| **Aorta (heart):** Mineralization | | **0** | **3** | **4** | **0** | **0** | **0** |
| | minimal | 0 | 1 | 2 | 0 | 0 | 0 |
| | mild | 0 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| | severe | 0 | 2 | 0 | 0 | 0 | 0 |
| **Aorta (abdominal)(infusion site):** Mineralization | | **0** | **3** | **3** | **0** | **0** | **0** |
| | mild | 0 | 1 | 0 | 0 | 0 | 0 |
| | moderate | 0 | 1 | 0 | 0 | 0 | 0 |
| | severe | 0 | 1 | 3 | 0 | 0 | 0 |

Stomach:
Main study
Mineralization was noted in the stomach in 2 HD Zemplar treated males. See Table below from the sponsor:



Reference ID: 3028604

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| Number of animals examined | | 10 | 10 | 10 | 10 | 10 | 10 |
| Tissue: Finding | Severity | | | | | | |
| Stomach: Mineralization, multifocal | | 0 | 0 | 2 | 0 | 0 | 0 |
| | minimal | 0 | 0 | 2 | 0 | 0 | 0 |

Recovery study

Mineralization was still reported at HD treated males (Zemplar, 1; HP, 2). Compared to the main study, the HP-treated males developed mineralization with delay compared to the Zemplar-treated males. This finding in one of the HP-treated males at HD correlated with the macroscopic finding of thickening in stomach area (thickening issue was not reported in the Main study). See Table below from the sponsor:

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| Number of animals examined | | 5 | 5 | 5 | 5 | 5 | 5 |
| Tissue: Finding | Severity | | | | | | |
| Stomach: Mineralization, multifocal | | 0 | 2 | 1 | 0 | 0 | 0 |
| | minimal | 0 | 1 | 1 | 0 | 0 | 0 |
| | severe | 0 | 1 | 0 | 0 | 0 | 0 |

Mammary gland

Main study

Mineralization was observed in 3 males at HD in Zemplar-treated animals. See Table below from the sponsor:

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| Number of animals examined | | 10 | 10 | 10 | 10 | 10 | 10 |
| Tissue: Finding | Severity | | | | | | |
| Mammary gland: Mineralization | | 0 | 0 | 3 | 0 | 0 | 0 |

Recovery study:

Mineralization of mammary gland was still present in 1 male at HD in Zemplar-treated animals and in 1 male at HD in HP-treated rat. Again, it appeared that there was delayed in onset of the mineralization in HP-treated males. See Table below from the sponsor:

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| Dose Level (µg/kg/dose) | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| Number of animals examined | | 5 | 5 | 5 | 5 | 5 | 5 |
| Mammary gland: Mineralization | | 0 | 1 | 1 | 0 | 0 | 0 |
| | minimal | 0 | 1 | 1 | 0 | 0 | 0 |

Kidney

Main study

- Unilateral or bilateral tubular basophilia was reported as following in: HP (control: 5 M; 1 F; HD: 9 M; 3 F) and Zemplar: (HD 9 M; 4 F).
- Tubular dilatation was reported as following: HP (HD: 4 M; 2 F) and Zemplar (HD: 6 M; 4 F).
- Mineralization was observed only at HD in males as following: HP (3) and Zemplar (5). See Table below from the sponsor:



Reference ID: 3028604

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **10** | **10** | **10** | **10** | **10** | **10** |
| **Kidneys:** Basophilia, tubular basophilia | | **5** | **9** | **9** | **1** | **3** | **4** |
| | minimal | 5 | 8 | 7 | 1 | 3 | 4 |
| | mild | 0 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 1 | 1 | 0 | 0 | 0 |
| **Kidneys:** Dilatation, tubular | | **0** | **4** | **6** | **0** | **2** | **4** |
| | minimal | 0 | 3 | 4 | 0 | 2 | 4 |
| | mild | 0 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 1 | 1 | 0 | 0 | 0 |
| **Kidneys:** Mineralization | | 0 | 3 | 5 | 0 | 0 | 0 |
| | minimal | 0 | 3 | 5 | 0 | 0 | 0 |

Recovery study:

- Tubular basophilia was still reported in HD treated animals: HP: Control (2M); HD (5M; 3 F); and Zemplar, HD (4M; 2F); this incidence was correlated with the macroscopic finding of irregular surface/pale discoloration in these animals.
- Tubular dilatation was still reported at HD treated animals: HP (3M; 2 F) and Zemplar (3 M; 1 F).
- Mineralization was observed at HD treated males: HP (3) and Zemplar (2).

See Table below from the sponsor:

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **5** | **5** | **5** | **5** | **5** | **5** |
| **Kidneys:** Basophilia, tubular | | **2** | **5** | **4** | **0** | **3** | **2** |
| | minimal | 2 | 3 | 2 | 0 | 3 | 2 |
| | mild | 0 | 1 | 2 | 0 | 0 | 0 |
| | moderate | 0 | 1 | 0 | 0 | 0 | 0 |
| **Kidneys:** Dilatation, tubular | | **0** | **3** | **3** | **0** | **2** | **1** |
| | minimal | 0 | 1 | 1 | 0 | 2 | 1 |
| | mild | 0 | 1 | 2 | 0 | 0 | 0 |
| | moderate | 0 | 1 | 0 | 0 | 0 | 0 |
| **Kidneys:** Mineralization | | **0** | **3** | **2** | **0** | **0** | **0** |
| | minimal | 0 | 3 | 2 | 0 | 0 | 0 |

Infusion site

Main study:

Endothelial hyperplasia, mural thrombus and chronic inflammation were reported at infusion site which correlated with the macroscopic findings of pale or dark material with/without thickening in both genders. See Table below from the sponsor:

*Reviewer: for the infusion site, the total number for all changes that was reported by the sponsor did not correlate to the total number by adding cases for each incidence (Table below). The total number should be: Males: 0HS (15); 10H (16); 10Z (14); Females: 0HS (13); 10H (11); and 10 Z (10).*



Reference ID: 3028604

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **10** | **10** | **10** | **10** | **10** | **10** |
| **Infusion site:** | | **10** | **10** | **10** | **9** | **9** | **8** |
| Inflammation, chronic, vessel wall | minimal | 0 | 5 | 0 | 4 | 0 | 0 |
| | mild | 2 | 1 | 1 | 0 | 1 | 0 |
| | moderate | 1 | 0 | 0 | 0 | 0 | 0 |
| | severe | 0 | 0 | 0 | 0 | 0 | 2 |
| Thrombus, mural | minimal | 1 | 2 | 0 | 2 | 3 | 2 |
| | mild | 2 | 2 | 3 | 0 | 3 | 0 |
| | moderate | 3 | 1 | 2 | 0 | 0 | 1 |
| | severe | 1 | 0 | 3 | 0 | 0 | 2 |
| Endothelial hyperplasia | minimal | 3 | 5 | 5 | 6 | 3 | 3 |
| | mild | 2 | 0 | 0 | 1 | 1 | 0 |

Recovery study:
The endothelial hyperplasia, mural thrombus and chronic inflammation were still presented in all groups. These findings correlated with the pale or dark material/thickening observation at infusion site. See Table below from the sponsor:
*Reviewer: for the infusion site, the total number for all changes that was reported by the sponsor did not correlate to the total number by adding cases for each incidence (Table below). The total number should be: Males: 0HS (2); 10H (8); 10Z (7); Females: 0HS (4); 10H (4); and 10 Z (8).*

| Sex | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose Level (µg/kg/dose)** | | 0HS | 10 H | 10 Z | 0HS | 10 H | 10 Z |
| **Number of animals examined** | | **5** | **5** | **5** | **5** | **5** | **5** |
| **Infusion site:** | | **2** | **4** | **5** | **3** | **4** | **4** |
| Inflammation, chronic, vessel wall | minimal | 1 | 0 | 0 | 1 | 3 | 1 |
| | mild | 0 | 1 | 0 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| Thrombus, mural | minimal | 0 | 2 | 1 | 0 | 0 | 3 |
| | mild | 1 | 0 | 1 | 0 | 0 | 0 |
| | moderate | 0 | 0 | 1 | 2 | 0 | 1 |
| Endothelial hyperplasia | minimal | 0 | 1 | 0 | 1 | 1 | 2 |
| | mild | 0 | 1 | 2 | 0 | 0 | 0 |
| | minimal | 0 | 3 | 2 | 0 | 0 | 0 |

Other microscopic findings:
Two males in HP (1/HD) and Zemplar (1/control) showed firm/mottled liver changes that correlated with the infarction/chronic inflammation (probably procedure-related).

See Tables below from the sponsor for microscopic findings:



Reference ID: 3028604

| Dose (µg/kg/dose) | 0 (Control HS) | | 10 (Hospira High) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|
| Number of Animals Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| Number of animals examined | M: 10 | F: 10 | M: 10 | F: 10 | M: 10 | F: 10 |
| **Histopathology – Day 28**<br>**Aorta:** Mineralization, thoracic | 0 | 0 | 0 | 0 | 2 | 0 |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 0 | 0 | 1 | 0 |
| **Heart:** Mineralization, aorta | 0 | 0 | 0 | 0 | 2 | 0 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 0 | 0 | 1 | 0 |
| **Kidneys:** Basophilia, tubular basophilia | 5 | 1 | 9 | 3 | 9 | 4 |
| minimal | 5 | 1 | 8 | 3 | 7 | 4 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 1 | 0 | 1 | 0 |
| **Kidneys:** Dilatation, tubular | 0 | 0 | 4 | 2 | 6 | 4 |
| minimal | 0 | 0 | 3 | 2 | 4 | 4 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 1 | 0 | 1 | 0 |
| **Kidneys:** Mineralization | 0 | 0 | 3 | 0 | 5 | 0 |
| minimal | 0 | 0 | 3 | 0 | 5 | 0 |
| **Mammary gland:** Mineralization | 0 | 0 | 0 | 0 | 3 | 0 |
| minimal | 0 | 0 | 0 | 0 | 3 | 0 |
| **Stomach:** Mineralization, multifocal | 0 | 0 | 0 | 0 | 2 | 0 |
| minimal | 0 | 0 | 0 | 0 | 2 | 0 |

| Dose (µg/kg/dose) | 0 (Control HS) | | 10 (Hospira High) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|
| Number of Animals Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| Number of animals examined | M: 10 | F: 10 | M: 10 | F: 10 | M: 10 | F: 10 |
| **Histopathology – Day 28 (cont'd)**<br>Mineralization, abdominal aorta | 0 | 0 | 1 | 0 | 3 | 0 |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 2 | 0 |
| **Infusion site:** | 10 | 9 | 10 | 9 | 10 | 8 |
| Inflammation, chronic, vessel wall | 3 | 4 | 6 | 1 | 1 | 2 |
| minimal | 0 | 4 | 5 | 0 | 0 | 0 |
| mild | 2 | 0 | 1 | 1 | 1 | 0 |
| moderate | 1 | 0 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 0 | 0 | 0 | 2 |
| Thrombus, mural | 7 | 2 | 5 | 6 | 8 | 5 |
| minimal | 1 | 2 | 2 | 3 | 0 | 2 |
| mild | 2 | 0 | 2 | 3 | 3 | 0 |
| moderate | 3 | 0 | 1 | 0 | 2 | 1 |
| severe | 1 | 0 | 0 | 0 | 3 | 2 |
| Endothelial hyperplasia | 5 | 7 | 5 | 4 | 5 | 3 |
| minimal | 3 | 6 | 5 | 3 | 5 | 3 |
| mild | 2 | 1 | 0 | 1 | 0 | 0 |

M Male F Female NA Not applicable

| Dose (µg/kg/dose) | 0 (Control HS) | | 10 (Hospira High) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|
| Number of Animals Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| Additional Examinations (Recovery Period) | | | | | | |
| Number of animals examined | M: 5 | F: 5 | M: 5 | F: 5 | M: 5 | F: 5 |
| Histopathology – Day 42 | | | | | | |
| Aorta: Mineralization, thoracic | 0 | 0 | 2 | 0 | 3 | 0 |
| minimal | 0 | 0 | 0 | 0 | 2 | 0 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| severe | 0 | 0 | 2 | 0 | 0 | 0 |
| Heart: Mineralization, aorta | 0 | 0 | 3 | 0 | 4 | 0 |
| minimal | 0 | 0 | 1 | 0 | 2 | 0 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 0 | 0 | 1 | 0 |
| severe | 0 | 0 | 2 | 0 | 0 | 0 |
| Kidneys: Basophilia, tubular | 2 | 0 | 5 | 3 | 4 | 2 |
| minimal | 2 | 0 | 3 | 3 | 2 | 2 |
| mild | 0 | 0 | 1 | 0 | 2 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| Kidneys: Dilatation, tubular | 0 | 0 | 3 | 2 | 3 | 1 |
| minimal | 0 | 0 | 1 | 2 | 1 | 1 |
| mild | 0 | 0 | 1 | 0 | 2 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| Kidneys: Mineralization | 0 | 0 | 3 | 0 | 2 | 0 |
| minimal | 0 | 0 | 3 | 0 | 2 | 0 |
| Mammary gland: Mineralization | 0 | 0 | 1 | 0 | 1 | 0 |
| minimal | 0 | 0 | 1 | 0 | 1 | 0 |
| Stomach: Mineralization, multifocal | 0 | 0 | 2 | 0 | 1 | 0 |
| minimal | 0 | 0 | 1 | 0 | 1 | 0 |
| severe | 0 | 0 | 1 | 0 | 0 | 0 |
| Mineralization, abdominal aorta | 0 | 0 | 3 | 0 | 3 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 |
| severe | 0 | 0 | 1 | 0 | 3 | 0 |

M Male F Female

| Dose (µg/kg/dose) | 0 (Control HS) | | 10 (Hospira High) | | 10 (Zemplar® High) | |
|---|---|---|---|---|---|---|
| Number of Animals Main<br>Recovery | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 | M: 10<br>M: 5 | F: 10<br>F: 5 |
| Additional Examinations (Recovery Period)- Cont'd | | | | | | |
| Number of animals examined | M: 5 | F: 5 | M: 5 | F: 5 | M: 5 | F: 5 |
| Histopathology – Day 42 | | | | | | |
| Infusion site: | 2 | 3 | 4 | 4 | 5 | 4 |
| Inflammation, chronic, vessel wall | 1 | 1 | 1 | 3 | 0 | 2 |
| minimal | 1 | 1 | 0 | 3 | 0 | 1 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| Thrombus, mural | 1 | 2 | 2 | 0 | 3 | 4 |
| minimal | 0 | 0 | 2 | 0 | 1 | 3 |
| mild | 1 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 2 | 0 | 0 | 1 | 1 |
| Endothelial hyperplasia | 0 | 1 | 2 | 1 | 2 | 2 |
| Minimal | 0 | 1 | 1 | 1 | 0 | 2 |
| Mild | 0 | 0 | 1 | 0 | 2 | 0 |

M Male F Female

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| ADRENALS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| AORTA; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 0 | 8 |
| Von kossa, negative | 1 | 0 | 0 | 1 | 0 | 1 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 1 |
| Mineralization, thoracic | (0) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| BRAIN; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| CECUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| COLON; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| EPIDIDYMIDES; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Cell debris | (0) | (0) | (0) | (0) | (0) | (1) |
| present | 0 | 0 | 0 | 0 | 0 | 1 |
| Oligospermia/aspermia | (0) | (0) | (0) | (0) | (0) | (1) |
| severe | 0 | 0 | 0 | 0 | 0 | 1 |
| ESOPHAGUS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| ESOPHAGUS; (continued) | | | | | | |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| EYES; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Dysplasia, retinal, focal | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| Inflammation, conjunctival, focal | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| FEMUR & MARROW; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| HEART; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 6 | 0 | 0 | 7 | 0 | 5 |
| Inflammation, subacute, focal | (3) | (0) | (0) | (2) | (0) | (4) |
| minimal | 3 | 0 | 0 | 2 | 0 | 4 |
| Inflammation, adventitial, focal | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralization, aorta | (0) | (0) | (0) | (0) | (0) | (2) |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 2 |
| Von kossa, negative | 1 | 0 | 0 | 1 | 0 | 0 |
| KIDNEYS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (2) | (10) |
| Within Normal Limits | 3 | 0 | 0 | 1 | 0 | 1 |
| Basophilia, tubular | (5) | (0) | (0) | (9) | (2) | (9) |
| minimal | 5 | 0 | 0 | 8 | 2 | 7 |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| moderate | 0 | 0 | 0 | 1 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| KIDNEYS; (continued) | | | | | | |
| Cast, hyaline | (1) | (0) | (0) | (1) | (0) | (0) |
| minimal | 1 | 0 | 0 | 1 | 0 | 0 |
| Cell infiltrate, interstitial | (2) | (0) | (0) | (0) | (1) | (0) |
| minimal | 2 | 0 | 0 | 0 | 1 | 0 |
| Dilatation, pelvic | (1) | (0) | (0) | (0) | (0) | (0) |
| mild | 1 | 0 | 0 | 0 | 0 | 0 |
| Dilatation, tubular | (0) | (0) | (0) | (4) | (0) | (6) |
| minimal | 0 | 0 | 0 | 3 | 0 | 4 |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| moderate | 0 | 0 | 0 | 1 | 0 | 1 |
| Mineralization | (0) | (0) | (0) | (3) | (0) | (5) |
| minimal | 0 | 0 | 0 | 3 | 0 | 5 |
| Congestion | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 |
| Hyaline droplet, tubular epithelium | (0) | (0) | (0) | (0) | (0) | (1) |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrosis, focal | (0) | (0) | (0) | (0) | (1) | (0) |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 |
| Inflammation, subacute, pelvis | (0) | (0) | (0) | (2) | (0) | (0) |
| minimal | 0 | 0 | 0 | 2 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 0 | 2 | 0 | 1 |
| Von kossa, negative | 2 | 0 | 0 | 1 | 0 | 1 |
| Von kossa positive (background finding) | 0 | 0 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 0 | 9 |
| Congestion | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |
| Hematopoiesis, extramedullary | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| Microgranuloma | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LIVER; (continued) | | | | | | |
| Fusion, lobular | (1) | (0) | (0) | (0) | (0) | (0) |
| present | 1 | 0 | 0 | 0 | 0 | 0 |
| Necrosis, focal | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| LUNGS; | | | | | | |
| Examined | (10) | (1) | (1) | (10) | (2) | (10) |
| Within Normal Limits | 8 | 0 | 0 | 7 | 0 | 7 |
| Histiocytosis, alveolar | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| Microgranuloma | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage, focal | (2) | (1) | (1) | (3) | (2) | (2) |
| minimal | 2 | 1 | 1 | 3 | 2 | 2 |
| LN, BRONCHIAL; | | | | | | |
| Examined | (1) | (3) | (2) | (2) | (2) | (3) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (1) | (3) | (2) | (2) | (2) | (3) |
| minimal | 0 | 3 | 2 | 1 | 2 | 2 |
| mild | 1 | 0 | 0 | 1 | 0 | 1 |
| LN, ILIAC; | | | | | | |
| Examined | (1) | (0) | (1) | (0) | (1) | (3) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | (0) | (0) | (1) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (1) | (0) | (1) | (2) |
| minimal | 0 | 0 | 1 | 0 | 0 | 2 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| Plasmacytosis | (1) | (0) | (0) | (0) | (0) | (1) |
| mild | 1 | 0 | 0 | 0 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, MANDIBULAR; | | | | | | |
| Examined | (10) | (0) | (1) | (10) | (1) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 8 |
| Hemorrhage | (0) | (0) | (1) | (0) | (1) | (1) |
| minimal | 0 | 0 | 0 | 0 | 1 | 1 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| Erythrophagocytosis | (0) | (0) | (1) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| LN, MEDIASTINAL; | | | | | | |
| Examined | (0) | (0) | (2) | (2) | (2) | (0) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | (0) | (0) | (2) | (1) | (1) | (0) |
| minimal | 0 | 0 | 1 | 1 | 1 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (1) | (1) | (1) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 1 | 0 |
| Pigment, brown | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| LN, MESENTERIC; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| LN, PANCREATIC; | | | | | | |
| Examined | (0) | (0) | (0) | (0) | (0) | (1) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, RENAL; | | | | | | |
| Examined | (0) | (0) | (0) | (0) | (0) | (0) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| Plasmacytosis | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| MAMMARY GLAND; | | | | | | |
| Examined | (9) | (0) | (0) | (10) | (0) | (9) |
| Within Normal Limits | 8 | 0 | 0 | 10 | 0 | 6 |
| Not Examined: Not Present On The Section | 1 | 0 | 0 | 0 | 0 | 1 |
| Mineralization | (0) | (0) | (0) | (0) | (0) | (3) |
| minimal | 0 | 0 | 0 | 0 | 0 | 3 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 3 |
| Von kossa, negative | 1 | 0 | 0 | 0 | 0 | 0 |
| OPTIC NERVES; | | | | | | |
| Examined | (6) | (0) | (0) | (9) | (0) | (10) |
| Within Normal Limits | 6 | 0 | 0 | 9 | 0 | 10 |
| Not Examined: Not Present On The Section | 4 | 0 | 0 | 1 | 0 | 0 |
| OVARIES; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| PANCREAS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Necrosis, focal | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| PARATHYROIDS; | | | | | | |
| Examined | (9) | (0) | (0) | (9) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 0 | 10 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| PARATHYROIDS; (continued) | | | | | | |
| Not Examined: Not Present On The Section | 1 | 0 | 0 | 1 | 0 | 0 |
| PITUITARY; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| PROSTATE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 4 | 0 | 0 | 7 | 0 | 8 |
| Inflammation, subacute, interstitial | (6) | (0) | (0) | (3) | (0) | (2) |
| minimal | 3 | 0 | 0 | 1 | 0 | 0 |
| mild | 3 | 0 | 0 | 2 | 0 | 2 |
| RECTUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SG, MANDIBULAR; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SCIATIC NERVE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SEMINAL VESICLES; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SKELETAL MUSCLE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 9 | 0 | 8 |
| Inflammation, subacute, focal | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| SKELETAL MUSCLE; (continued) | | | | | | |
| Necrosis, focal | (0) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 0 | 0 | 0 | 2 |
| SKIN & SUBCUTIS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 10 | 0 | 8 |
| Catheter track | (1) | (0) | (0) | (0) | (0) | (2) |
| present | 1 | 0 | 0 | 0 | 0 | 2 |
| Inflammation, chronic, subcutis | (1) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 1 | 0 | 0 | 0 | 0 | 2 |
| Edema, subcutaneous | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| Inflammation, chronic-active, subcutis | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| DUODENUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| ILEUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (9) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Not Examined: No Section | 0 | 0 | 0 | 0 | 0 | 1 |
| JEJUNUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SC, CERVICAL; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| SPLEEN; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Hematopoiesis, increased | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrosis, capsular, focal | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| STERNUM & MARROW; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| STOMACH; | | | | | | |
| Examined | (10) | (0) | (1) | (10) | (1) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 1 | 8 |
| Hemorrhage | (0) | (0) | (1) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| Mineralization, multifocal | (0) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 0 | 0 | 0 | 2 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 1 |
| Von kossa, negative | 1 | 0 | 0 | 1 | 0 | 1 |
| TESTES; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Degeneration/atrophy, seminiferous tubule | (0) | (0) | (0) | (0) | (0) | (1) |
| moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| THYMUS; | | | | | | |
| Examined | (10) | (0) | (2) | (10) | (4) | (10) |
| Within Normal Limits | 8 | 0 | 0 | 7 | 0 | 6 |
| Congestion/hemorrhage | (2) | (0) | (2) | (2) | (4) | (3) |
| minimal | 1 | 0 | 2 | 1 | 4 | 1 |
| mild | 1 | 0 | 0 | 1 | 0 | 2 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| THYMUS; (continued) | | | | | | |
| Depletion, lymphoid | (0) | (0) | (0) | (1) | (0) | (1) |
| minimal | 0 | 0 | 0 | 1 | 0 | 1 |
| THYROID GLAND; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| TONGUE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 0 | 9 |
| Inflammation, chronic, focal | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |
| Von kossa, negative | 1 | 0 | 0 | 0 | 0 | 1 |
| TRACHEA; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| URINARY BLADDER; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Not Examined: No Section | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, urothelial | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| UTERUS; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| VAGINA; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| Not Examined: No Section | - | - | - | - | - | - |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

| Removal Reason: Terminal | MALES Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
|---|---|---|---|---|---|---|
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| INFUSION SITE; | | | | | | |
| Examined | (10) | (7) | (4) | (10) | (6) | (10) |
| Within Normal Limits | 0 | 1 | 0 | 0 | 0 | 0 |
| Hyperplasia, endothelial | (5) | (0) | (0) | (5) | (3) | (5) |
| minimal | 3 | 0 | 0 | 5 | 2 | 5 |
| mild | 2 | 0 | 0 | 0 | 1 | 0 |
| Thrombus, mural | (7) | (6) | (4) | (5) | (4) | (8) |
| minimal | 1 | 3 | 2 | 2 | 3 | 0 |
| mild | 2 | 0 | 0 | 2 | 1 | 3 |
| moderate | 3 | 2 | 2 | 1 | 0 | 2 |
| severe | 1 | 1 | 0 | 0 | 0 | 3 |
| Inflammation, chronic, vessel wall | (3) | (1) | (0) | (6) | (0) | (1) |
| minimal | 0 | 0 | 0 | 5 | 0 | 0 |
| mild | 2 | 0 | 0 | 1 | 0 | 1 |
| moderate | 1 | 0 | 0 | 0 | 0 | 0 |
| severe | 0 | 1 | 0 | 0 | 0 | 0 |
| Mineralization, abdominal aorta | (0) | (0) | (0) | (1) | (0) | (3) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 2 |
| Edema | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| Von kossa, positive | 0 | 0 | 0 | 1 | 0 | 2 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:

Observations: Neo-Plastic and Non Neo-Plastic

| Removal Reason: Terminal | FEMALES Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
|---|---|---|---|---|---|---|
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| ADRENALS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| AORTA; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Von kossa, negative | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralization, thoracic | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| BRAIN; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| CECUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| COLON; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| EPIDIDYMIDES; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| Cell debris | (-) | (-) | (-) | (-) | (-) | (-) |
| present | - | - | - | - | - | - |
| Oligospermia/aspermia | (-) | (-) | (-) | (-) | (-) | (-) |
| severe | - | - | - | - | - | - |
| ESOPHAGUS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| KIDNEYS; (continued) | | | | | | |
| Cast, hyaline | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |
| Cell infiltrate, interstitial | (2) | (0) | (0) | (1) | (0) | (1) |
| minimal | 2 | 0 | 0 | 1 | 0 | 1 |
| Dilatation, pelvic | (0) | (0) | (0) | (0) | (1) | (0) |
| mild | 0 | 0 | 0 | 0 | 1 | 0 |
| Dilatation, tubular | (0) | (0) | (0) | (2) | (0) | (4) |
| minimal | 0 | 0 | 0 | 2 | 0 | 4 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralization | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Congestion | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyaline droplet, tubular epithelium | (0) | (0) | (0) | (0) | (0) | (0) |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| Fibrosis, focal | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 |
| Inflammation, subacute, pelvis | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa positive (background finding) | 1 | 0 | 0 | 2 | 0 | 3 |
| LIVER; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 8 | 0 | 0 | 8 | 0 | 9 |
| Congestion | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 |
| Hematopoiesis, extramedullary | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Microgranuloma | (0) | (0) | (0) | (2) | (0) | (1) |
| minimal | 0 | 0 | 0 | 1 | 0 | 1 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, MANDIBULAR; | | | | | | |
| Examined | (10) | (1) | (3) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 9 | 0 | 10 |
| Hemorrhage | (0) | (0) | (1) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (1) | (3) | (1) | (0) | (0) |
| mild | 0 | 1 | 3 | 1 | 0 | 0 |
| Erythrophagocytosis | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| LN, MEDIASTINAL; | | | | | | |
| Examined | (0) | (0) | (1) | (2) | (0) | (3) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (1) | (1) | (0) | (3) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 3 |
| Pigment, brown | (0) | (0) | (0) | (1) | (0) | (0) |
| mild | 0 | 0 | 0 | 1 | 0 | 0 |
| LN, MESENTERIC; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| LN, PANCREATIC; | | | | | | |
| Examined | (0) | (0) | (0) | (0) | (0) | (1) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, RENAL; | | | | | | |
| Examined | (0) | (1) | (0) | (0) | (0) | (1) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 1 |
| Plasmacytosis | (0) | (1) | (0) | (0) | (0) | (0) |
| mild | 0 | 1 | 0 | 0 | 0 | 0 |
| MAMMARY GLAND; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Not Examined: Not Present On The Section | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralization | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 0 | 0 | 0 |
| OPTIC NERVES; | | | | | | |
| Examined | (9) | (0) | (0) | (7) | (0) | (7) |
| Within Normal Limits | 9 | 0 | 0 | 7 | 0 | 7 |
| Not Examined: Not Present On The Section | 1 | 0 | 0 | 3 | 0 | 3 |
| OVARIES; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| PANCREAS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Necrosis, focal | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| PARATHYROIDS; | | | | | | |
| Examined | (9) | (0) | (0) | (10) | (0) | (9) |
| Within Normal Limits | 9 | 0 | 0 | 10 | 0 | 9 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| PARATHYROIDS; (continued) | | | | | | |
| Not Examined: Not Present On The Section | 1 | 0 | 0 | 0 | 0 | 1 |
| PITUITARY; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| PROSTATE; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| Inflammation, subacute, interstitial | (-) | (-) | (-) | (-) | (-) | (-) |
| minimal | - | - | - | - | - | - |
| mild | - | - | - | - | - | - |
| RECTUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SG, MANDIBULAR; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SCIATIC NERVE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SEMINAL VESICLES; | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (-) | (-) |
| Within Normal Limits | - | - | - | - | - | - |
| SKELETAL MUSCLE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 10 | 0 | 9 |
| Inflammation, subacute, focal | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 1 |

## Aorta

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY Date: 09/02/11

| Observations: Neo-Plastic and Non Neo-Plastic | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| SKELETAL MUSCLE; (continued) | | | | | | |
| Necrosis, focal | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 |
| SKIN & SUBCUTIS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 7 | 0 | 0 | 6 | 0 | 9 |
| Catheter track | (1) | (0) | (0) | (3) | (0) | (1) |
| present | 1 | 0 | 0 | 3 | 0 | 1 |
| Inflammation, chronic, subcutis | (2) | (0) | (0) | (1) | (0) | (1) |
| minimal | 1 | 0 | 0 | 0 | 0 | 1 |
| mild | 1 | 0 | 0 | 1 | 0 | 0 |
| Edema, subcutaneous | (1) | (0) | (0) | (2) | (0) | (0) |
| mild | 1 | 0 | 0 | 2 | 0 | 0 |
| Inflammation, chronic-active, subcutis | (0) | (0) | (0) | (2) | (0) | (0) |
| mild | 0 | 0 | 0 | 2 | 0 | 0 |
| DUODENUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| ILEUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Not Examined: No Section | 0 | 0 | 0 | 0 | 0 | 0 |
| JEJUNUM; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| SC, CERVICAL; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| Removal Reason: Terminal | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| THYMUS; (continued) | | | | | | |
| Depletion, lymphoid | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| THYROID GLAND; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| TONGUE; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| Inflammation, chronic, focal | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 0 | 0 | 0 |
| TRACHEA; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| URINARY BLADDER; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (9) |
| Within Normal Limits | 10 | 0 | 0 | 9 | 0 | 8 |
| Not Examined: No Section | 0 | 0 | 0 | 0 | 0 | 1 |
| Hyperplasia, urothelial | (0) | (0) | (0) | (1) | (0) | (1) |
| minimal | 0 | 0 | 0 | 1 | 0 | 1 |
| UTERUS; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 10 |
| VAGINA; | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (0) | (9) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 0 | 9 |
| Not Examined: No Section | 0 | 0 | 0 | 0 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| INFUSION SITE; | | | | | | |
| Examined | (10) | (4) | (4) | (10) | (5) | (10) |
| Within Normal Limits | 1 | 0 | 1 | 1 | 0 | 2 |
| Hyperplasia, endothelial | (7) | (2) | (2) | (4) | (1) | (3) |
| minimal | 6 | 2 | 0 | 3 | 0 | 3 |
| mild | 1 | 0 | 2 | 1 | 1 | 0 |
| Thrombus, mural | (2) | (2) | (3) | (6) | (5) | (5) |
| minimal | 2 | 0 | 1 | 3 | 2 | 2 |
| mild | 0 | 1 | 2 | 3 | 1 | 0 |
| moderate | 0 | 0 | 0 | 0 | 2 | 1 |
| severe | 0 | 1 | 0 | 0 | 0 | 2 |
| Inflammation, chronic, vessel wall | (4) | (2) | (0) | (2) | (1) | (2) |
| minimal | 4 | 0 | 0 | 0 | 1 | 0 |
| mild | 0 | 1 | 0 | 2 | 0 | 0 |
| moderate | 0 | 1 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 0 | 0 | 0 | 2 |
| Mineralization, abdominal aorta | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| Edema | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 0 | 0 | 0 | 0 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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Observations: Neo-Plastic and Non Neo-Plastic

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| ADRENALS; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 1 | 5 | 5 | 5 | 0 | 5 | 5 |
| AORTA; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 3 | 2 | 5 | 0 | 5 | 4 |
| Von kossa, negative | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Von kossa, positive | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| Mineralization, thoracic | (0) | (0) | (2) | (3) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| BRAIN; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| CECUM; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| COLON; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| EPIDIDYMIDES; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5 | 0 | 5 | 5 | - | - | - | - |
| Cell debris | (0) | (1) | (0) | (0) | (-) | (-) | (-) | (-) |
| present | 0 | 1 | 0 | 0 | - | - | - | - |
| Oligospermia/aspermia | (0) | (1) | (0) | (0) | (-) | (-) | (-) | (-) |
| severe | 0 | 1 | 0 | 0 | - | - | - | - |

GROUP 1: Control HS
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| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| ESOPHAGUS; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| EYES; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| FEMUR & MARROW; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| HEART; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 1 | 0 | 1 | 1 | 5 | 0 | 5 | 4 |
| Inflammation, subacute, focal | (4) | (0) | (1) | (1) | (0) | (0) | (0) | (0) |
| minimal | 4 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Mineralization, aorta | (0) | (0) | (3) | (4) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| KIDNEYS; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 3 | 0 | 0 | 0 | 5 | 0 | 1 | 3 |
| Basophilia, tubular | (2) | (0) | (5) | (4) | (0) | (0) | (3) | (2) |
| minimal | 2 | 0 | 3 | 2 | 0 | 0 | 3 | 2 |
| mild | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Cell infiltrate, interstitial | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| KIDNEYS; (continued) | | | | | | | | |
| Dilatation, pelvic | (0) | (1) | (1) | (1) | (0) | (0) | (1) | (0) |
| minimal | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Dilatation, tubular | (0) | (0) | (3) | (3) | (0) | (0) | (2) | (1) |
| minimal | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 |
| mild | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Mineralization | (0) | (0) | (3) | (2) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 |
| Fibrosis, focal | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Inflammation, subacute, pelvis | (0) | (0) | (0) | (0) | (0) | (0) | (2) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Von kossa, positive | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 3 | 0 | 3 | 4 | 4 | 0 | 3 | 2 |
| Hematopoiesis, extramedullary | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Microgranuloma | (1) | (0) | (1) | (0) | (1) | (0) | (2) | (2) |
| minimal | 1 | 0 | 1 | 0 | 1 | 0 | 2 | 2 |
| Necrosis, focal | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Fatty change, macrovesicular | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Inflammation, chronic, portal/capsular | (0) | (1) | (1) | (0) | (0) | (0) | (0) | (0) |
| severe | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Infarct, lobular | (0) | (1) | (1) | (0) | (0) | (0) | (0) | (0) |
| severe | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| LUNGS; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 2 | 1 | 5 | 0 | 5 | 4 |
| Histiocytosis, alveolar | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hemorrhage, focal | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Inflammation, chronic, pleural/subpleural, focal | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Thrombosis, mural | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| LN, BRONCHIAL; | | | | | | | | |
| Examined | (0) | (0) | (1) | (1) | (0) | (0) | (1) | (0) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (1) | (1) | (0) | (0) | (1) | (0) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| LN, ILIAC; | | | | | | | | |
| Examined | (0) | (0) | (2) | (1) | (0) | (1) | (1) | (0) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (0) | (2) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Plasmacytosis | (0) | (0) | (0) | (0) | (0) | (1) | (1) | (0) |
| mild | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| LN, MANDIBULAR; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 4 | 0 | 5 | 4 |
| Hyperplasia, lymphoid | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

GROUP 1: Control HS
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GROUPS 5 and 6: Zemplar®

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| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| LN, MANDIBULAR; (continued) | | | | | | | | |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| LN, MESENTERIC; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 4 | 5 | 0 | 5 | 5 |
| Hemorrhage/erythrophagocytosis | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LN, PANCREATIC; | | | | | | | | |
| Examined | (0) | (1) | (2) | (0) | (0) | (0) | (0) | (1) |
| Within Normal Limits | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, lymphoid | (0) | (1) | (2) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| MAMMARY GLAND; | | | | | | | | |
| Examined | (4) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 4 | 0 | 4 | 2 | 5 | 0 | 5 | 5 |
| Not Examined: Not Present On The Section | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralization | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| OPTIC NERVES; | | | | | | | | |
| Examined | (5) | (0) | (4) | (4) | (1) | (0) | (4) | (5) |
| Within Normal Limits | 5 | 0 | 4 | 4 | 1 | 0 | 4 | 5 |
| Not Examined: Not Present On The Section | 0 | 0 | 1 | 1 | 4 | 0 | 1 | 0 |
| OVARIES; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (5) | (0) | (5) | (5) |
| Within Normal Limits | - | - | - | - | 5 | 0 | 5 | 5 |
| PANCREAS; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:4

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| PANCREAS; (continued) | | | | | | | | |
| Within Normal Limits | 4 | 0 | 4 | 5 | 5 | 0 | 5 | 5 |
| Inflammation, subacute, focal | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atrophy, acinar, focal | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| PARATHYROIDS; | | | | | | | | |
| Examined | (5) | (0) | (5) | (4) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 4 | 5 | 0 | 5 | 5 |
| Not Examined: Not Present On The Section | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| PITUITARY; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 4 | 5 |
| Cyst, pars intermedia | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) |
| present | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| PROSTATE; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 3 | 0 | 3 | 4 | - | - | - | - |
| Inflammation, subacute, interstitial | (2) | (0) | (2) | (1) | (-) | (-) | (-) | (-) |
| minimal | 2 | 0 | 1 | 1 | - | - | - | - |
| mild | 0 | 0 | 1 | 0 | - | - | - | - |
| RECTUM; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| SG, MANDIBULAR; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| SCIATIC NERVE; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| SCIATIC NERVE; (continued) | | | | | | | | |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| SEMINAL VESICLES; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5 | 0 | 5 | 5 | - | - | - | - |
| SKELETAL MUSCLE; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| SKIN & SUBCUTIS; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 4 | 4 | 3 | 0 | 3 | 5 |
| Catheter track | (0) | (0) | (1) | (1) | (1) | (0) | (1) | (0) |
| present | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 |
| Inflammation, chronic, subcutis | (0) | (0) | (1) | (1) | (2) | (0) | (1) | (0) |
| minimal | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 |
| mild | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| moderate | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| DUODENUM; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| ILEUM; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| JEJUNUM; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 1 | 5 | 5 | 5 | 0 | 5 | 4 |
| Inflammation, chronic, peyers patch, focal | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Von kossa, negative | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| SC, CERVICAL; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| SPLEEN; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 4 | 0 | 3 | 5 | 5 | 0 | 5 | 5 |
| Hematopoiesis, increased | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Fibrosis, capsular, focal | (1) | (0) | (0) | (0) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STERNUM & MARROW; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| STOMACH; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 1 | 2 | 5 | 0 | 5 | 4 |
| Mineralization, multifocal | (0) | (0) | (2) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| Von kossa, negative | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 1 |
| TESTES; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5 | 0 | 5 | 5 | - | - | - | - |
| Degeneration/atrophy, seminiferous tubule | (0) | (1) | (0) | (0) | (-) | (-) | (-) | (-) |
| severe | 0 | 1 | 0 | 0 | - | - | - | - |
| Granuloma, spermatic | (0) | (1) | (0) | (0) | (-) | (-) | (-) | (-) |
| mild | 0 | 1 | 0 | 0 | - | - | - | - |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| THYMUS; | | | | | | | | |
| Examined | (5) | (1) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 4 | 3 | 5 | 0 | 5 | 5 |
| Congestion/hemorrhage | (0) | (1) | (1) | (2) | (0) | (0) | (0) | (0) |
| minimal | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| THYROID GLAND; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| TONGUE; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| TRACHEA; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 5 | 0 | 5 | 5 |
| URINARY BLADDER; | | | | | | | | |
| Examined | (5) | (0) | (5) | (5) | (5) | (0) | (5) | (5) |
| Within Normal Limits | 5 | 0 | 5 | 5 | 4 | 0 | 3 | 5 |
| Hyperplasia, urothelial | (0) | (0) | (0) | (0) | (1) | (0) | (2) | (0) |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| UTERUS; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (5) | (0) | (5) | (5) |
| Within Normal Limits | - | - | - | - | 5 | 0 | 5 | 5 |
| VAGINA; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (5) | (0) | (5) | (5) |
| Within Normal Limits | - | - | - | - | 5 | 0 | 5 | 5 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF HISTOPATHOLOGY

Date: 09/02/11 8:46

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reason: Recovery | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| INFUSION SITE; | | | | | | | | |
| Examined | (5) | (3) | (5) | (5) | (5) | (3) | (5) | (5) |
| Within Normal Limits | 3 | 1 | 1 | 0 | 2 | 0 | 1 | 1 |
| Hyperplasia, endothelial | (0) | (0) | (2) | (2) | (1) | (3) | (1) | (2) |
| minimal | 0 | 0 | 1 | 0 | 1 | 3 | 1 | 2 |
| mild | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| Thrombus, mural | (1) | (2) | (2) | (3) | (2) | (2) | (0) | (4) |
| minimal | 0 | 1 | 2 | 1 | 0 | 1 | 0 | 3 |
| mild | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| moderate | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 1 |
| Inflammation, chronic, vessel wall | (1) | (0) | (1) | (0) | (1) | (1) | (3) | (1) |
| minimal | 1 | 0 | 0 | 0 | 1 | 1 | 3 | 0 |
| mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mineralization, abdominal aorta | (0) | (0) | (3) | (3) | (0) | (0) | (0) | (0) |
| mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 |
| severe | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Von kossa, positive | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 |

**Toxicokinetics:**

There was no significant difference in the mean paricalcitol Cmax between Day 1 to Day 26 of treatment. It appears that there is higher paricalcitol exposure in male compared to female animals (male versus female ratios for $C_{max}$ and $AUC_{0-t}$ ranging from 0.92 to 2.26). Results from the accumulation ratios (0.87 to 1.11 for HP; 0.83 to 1.13 for Zemplar) suggested no accumulation for both products. See the Tables below from the sponsor for samples that were collected and TK analysis:

| Group number | No. of animals | | Pre-dose | Toxicokinetic Timepoints (Post-Dose) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | Females | | 0.5 h | 2 hr | 6 hr | 12 hr | 24 hr |
| 1 | 3 | - | | √ | | | | |
| 2 | 3 | - | | √ | | | | |
| 3 | 3 + | 3 + | √ | | √ | | √ | |
| | 3 # | 3 # | | √ | | √ | | √ |
| 4 | 3 + | 3 + | √ | | √ | | √ | |
| | 3 # | 3 # | | √ | | √ | | √ |
| 5 | 3 + | 3 + | √ | | √ | | √ | |
| | 3 # | 3 # | | √ | | √ | | √ |
| 6 | 3 + | 3 + | √ | | √ | | √ | |
| | 3 # | 3 # | | √ | | √ | | √ |

+: animals with the lowest identification numbers
#: animals with the highest identification numbers

**Table 2. Mean Toxicokinetic Data of Paricalcitol Hospira and Zemplar® from Rats Dosed 4 Weeks**

| Day | Dose (µg/kg/dose) | Sex | $AUC_{0-t}$ (h•ng/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | CLss/F (mL/h/kg) |
|---|---|---|---|---|---|---|
| 1 | Hospira 1.5 | Male | 32.35 | 8.05 | 0.50 | 46.37 |
| | | Female | 14.32 | 5.00 | 0.50 | 104.72 |
| | Hospira 10 | Male | 278.22 | 68.84 | 0.50 | 35.94 |
| | | Female | 157.98 | 52.05 | 0.50 | 63.30 |
| | Zemplar® 1.5 | Male | 30.63 | 7.90 | 0.50 | 48.98 |
| | | Female | 15.08 | 5.31 | 0.50 | 99.49 |
| | Zemplar® 10 | Male | 273.72 | 70.14 | 0.50 | 36.53 |
| | | Female | 171.56 | 56.50 | 0.50 | 58.29 |
| 26 | Hospira 1.5 | Male | 32.06 | 8.95 | 0.50 | 46.79 |
| | | Female | 15.07 | 4.94 | 0.50 | 99.54 |
| | Hospira 10 | Male | 250.30 | 60.23 | 0.50 | 39.95 |
| | | Female | 146.90 | 52.26 | 0.50 | 68.07 |
| | Zemplar® 1.5 | Male | 32.20 | 6.92 | 0.50 | 46.58 |
| | | Female | 16.93 | 5.84 | 0.50 | 88.60 |
| | Zemplar® 10 | Male | 230.40 | 58.49 | 0.50 | 43.40 |
| | | Female | 164.37 | 63.73 | 0.50 | 60.84 |

| Day | Sex | Group | Treatment | Dose (ug/kg/dose) | Tmax (h) | Cmax (ng/mL) | Cmin (ng/mL) | Cavg (ng/mL) | F1 (%) | CLss/F (mL/h/kg) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 3 | Hospira Low | 1.50 | 0.50 | 8.05 | 0.00 | 1.35 | 597.48 | 46.37 |
| | | 4 | Hospira High | 10.0 | 0.50 | 68.84 | 0.00 | 11.59 | 593.84 | 35.94 |
| | | 5 | Zemplar Low | 1.50 | 0.50 | 7.90 | 0.00 | 1.28 | 619.05 | 48.98 |
| | | 6 | Zemplar High | 10.0 | 0.50 | 70.14 | 0.00 | 11.40 | 615.03 | 36.53 |
| | F | 3 | Hospira Low | 1.50 | 0.50 | 5.00 | 0.00 | 0.60 | 838.35 | 104.72 |
| | | 4 | Hospira High | 10.0 | 0.50 | 52.05 | 0.00 | 6.58 | 790.66 | 63.30 |
| | | 5 | Zemplar Low | 1.50 | 0.50 | 5.31 | 0.00 | 0.63 | 845.83 | 99.49 |
| | | 6 | Zemplar High | 10.0 | 0.50 | 56.50 | 0.00 | 7.15 | 790.35 | 58.29 |
| 26 | M | 3 | Hospira Low | 1.50 | 0.50 | 8.95 | 0.00 | 1.34 | 670.29 | 46.79 |
| | | 4 | Hospira High | 10.0 | 0.50 | 60.23 | 0.17 | 10.43 | 575.82 | 39.95 |
| | | 5 | Zemplar Low | 1.50 | 0.50 | 6.92 | 0.00 | 1.34 | 515.98 | 46.58 |
| | | 6 | Zemplar High | 10.0 | 0.50 | 58.49 | 0.00 | 9.60 | 609.31 | 43.40 |
| | F | 3 | Hospira Low | 1.50 | 0.50 | 4.94 | 0.00 | 0.63 | 786.26 | 99.54 |
| | | 4 | Hospira High | 10.0 | 0.50 | 52.26 | 0.00 | 6.12 | 853.74 | 68.07 |
| | | 5 | Zemplar Low | 1.50 | 0.50 | 5.84 | 0.00 | 0.71 | 827.87 | 88.60 |
| | | 6 | Zemplar High | 10.0 | 0.50 | 63.73 | 0.00 | 6.85 | 930.54 | 60.84 |

| Day | Sex | Group | Treatment | Dose (ug/kg/dose) | AUClast (ng·h/mL) | AUC0-t (ng·h/mL) | AUCtau (ng·h/mL) |
|---|---|---|---|---|---|---|---|
| 1 | M | 3 | Hospira Low | 1.50 | 26.70 | 32.35 | . |
| | | 4 | Hospira High | 10.0 | 269.70 | 278.22 | . |
| | | 5 | Zemplar Low | 1.50 | 25.92 | 30.63 | . |
| | | 6 | Zemplar High | 10.0 | 267.48 | 273.72 | . |
| | F | 3 | Hospira Low | 1.50 | 13.29 | 14.32 | . |
| | | 4 | Hospira High | 10.0 | 150.16 | 157.98 | . |
| | | 5 | Zemplar Low | 1.50 | 9.15 | 15.08 | . |
| | | 6 | Zemplar High | 10.0 | 158.64 | 171.56 | . |
| 26 | M | 3 | Hospira Low | 1.50 | . | 32.06 | 32.06 |
| | | 4 | Hospira High | 10.0 | . | 250.30 | 250.30 |
| | | 5 | Zemplar Low | 1.50 | . | 32.20 | 32.20 |
| | | 6 | Zemplar High | 10.0 | . | 230.40 | 230.40 |
| | F | 3 | Hospira Low | 1.50 | . | 15.07 | 15.07 |
| | | 4 | Hospira High | 10.0 | . | 146.90 | 146.90 |
| | | 5 | Zemplar Low | 1.50 | . | 16.93 | 16.93 |
| | | 6 | Zemplar High | 10.0 | . | 164.37 | 164.37 |

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

Treatment of metabolic bone disease associated with chronic kidney disease needs the correction of abnormal PTH levels and normalization of calcium and phosphorus homeostasis. Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain ($D_2$) and the A (19-nor) ring which activates the vitamin D receptor in the parathyroid glands (without increasing the vitamin D receptor in the intestine) and up regulates the calcium sensing receptor in the parathyroid glands.

The safety profile of the Zemplar (NDA 020819) has been well established. Consequently, nonclinical (pharmacology, pharmacokinetics and toxicology) studies for the HP (2 and 5 ug/mL) solution are relying on the previous findings of the safety and efficacy for Zemplar.

A 4-week repeat dose toxicity study in Sprague Dawley rats with a 2-week recovery period was conducted to assess the potential toxicity as well as to compare TK and PD of the HP to the RLD. Results of this study presented a similar extent of pharmacological changes in both compounds (dose-related decreased in iPTH with a slight to moderate increase in serum calcium levels) with increases in the relative weights of the kidneys to the body weights in all HD treated animals and/or the relative weights of the adrenals to the body weights in the HD treated HP group. These changes were correlated with renal mineralization as well as renal tubular basophilia/ tubular dilation of the HD groups of both compounds. Since the product is designed for administration to ESRD patients on dialysis, the renal findings in normal rats are not clinically relevant. In males at HD groups, the mean body weight gains were (ss) lower (HP: 8.5%; RLD: 8.6%) compared to the control groups during the main study. In addition, there was higher paricalcitol exposure in males compared to females (male female ratios: 2.26). The higher paricalcitol exposure in males was correlated with higher incidences of soft tissues



Reference ID: 3028604

mineralization in treated males with both compounds. Noteworthy histopathology findings were related to soft tissues mineralization, and increased inflammation at the infusion site.

At HD groups, increased incidences of soft tissues mineralization in the different regions of the aorta and the stomach were reported for: the RLD males during both the main and the recovery studies; and for the HP-treated males only during the recovery study suggesting delayed effect in soft tissues mineralization with the new HP formulation. At the end of the study, soft tissues mineralization incidences were similar between two compounds. In addition, in the HD treated males in the HP group, the incidence of stomach mineralization correlated with the macroscopic finding of thickening in the stomach area.

The histopathological findings at the infusion site suggested significantly higher increased inflammation at the infusion site in the HP-treated males at HD compared to the RLD (60% vs. 10%). At the end of the study, inflammation at the infusion site was still higher in the HP-treated males (20%) compared to the RLD (0%). The higher incidence of inflammation at the infusion site might be due to the higher percentage of (b) (4) in the new HP formulation since the HP vehicle treated animals also showed higher incidences of inflammation at the infusion site during the main and the recovery studies compared to the RLD vehicle treated animals (main study: 40% vs. 20%; recovery study: 20% vs. 0%).

In Summary, findings of this study suggested differences in toxicity profiles between the HP and the RLD in following:

1. The delay in the onset of the soft tissues mineralization at different areas of the aorta and the stomach in the HD treated males given the HP compound. Although at the end of the recovery study (2 week) these incidences were almost similar to the HD treated RLD males, it is not known how incidences of soft tissues mineralization would manifest over a longer recovery time. Given that, the soft tissues mineralization can be prevented by monitoring the serum calcium in subjects during the clinical studies.
2. Increased inflammation at the infusion site was reported at HD in males given the HP compared to the RLD. In this study, rats received i.v. infusion of ~0.8 mL of the HP compound (hold 0.3 ml of (b) (4) The MRHD will be 7 mcg or 1.4 mL of HP formulation (hold ~0.6 ml (b) (4) Consequently, at the local site in humans, the (b) (4) concentration will be 2X more compared to treated rats. The increased inflammation at the local site could be an important safety concern for patients under dialysis with the AV fistulas.

Moreover, in the submitted NDA, it is not clear how the new HP formulation will be used during dialysis. P/T recommends additional animals studies for providing more safety information for the i.v. infusion of the new HP formulation. However, if the new HP formulation will be diluted before administration, then there will be less concerns with inflammation at the infusion site (for example by infusing inside the port of dialysis). In this case, the margin safety will be more than 100 fold for the systemic (b) (4) concentration in human compared to rats.



Reference ID: 3028604

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**Appendix:**
**Organ weights:**

TABLE 8a

GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:13:46

Day(s) Relative to Start Date

Sex: Male

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 498 [I] | 0.0731 [I] | 2.1669 [I] | 1.6354 [I] | 2.8971 [I] | 12.9603 [I] | 1.9234 [I] |
| 0 | SD | 74.9 | 0.01763 | 0.07427 | 0.22448 | 0.26721 | 2.17497 | 0.32288 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 3 | Mean | 504 | 0.0805 | 2.2054 | 1.6677 | 2.9461 | 12.8697 | 1.9986 |
| 1.5 | SD | 49.8 | 0.01286 | 0.08445 | 0.12859 | 0.27569 | 1.68448 | 0.17823 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 4 | Mean | 469 | 0.0956 [**2] | 2.1454 | 1.5654 | 2.9627 | 12.6940 | 1.9037 |
| 10 | SD | 47.2 | 0.00784 | 0.07165 | 0.11654 | 0.27770 | 1.65809 | 0.22683 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][** - Statistical Test: Dunnett 2 Sided p < 0.01]

GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:13:46

Day(s) Relative to Start Date

Sex: Male

| | | Pituitary (g) GEN AN (AUTO) | Prostate (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Testes (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 0.0140 [I] | 1.0635 [I] | 1.1550 [I] | 3.6863 [I] | 0.4687 [L] | 0.0234 [I] |
| 0 | SD | 0.00228 | 0.19665 | 0.36214 | 0.35227 | 0.09438 | 0.00360 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 3 | Mean | 0.0161 [*2] | 1.1027 | 1.0853 | 3.6135 | 0.4686 | 0.0251 |
| 1.5 | SD | 0.00224 | 0.14541 | 0.14734 | 0.32931 | 0.14025 | 0.00539 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 4 | Mean | 0.0140 | 1.0763 | 0.9944 | 3.7608 | 0.3795 | 0.0234 |
| 10 | SD | 0.00128 | 0.18065 | 0.13630 | 0.14354 | 0.07648 | 0.00419 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][* - Statistical Test: Dunnett 2 Sided p < 0.05]
[3][L - Automatic Transformation Selected: Log]

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TABLE 8a

GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:13:46

Day(s) Relative to Start Date

Sex: Female

| | | Ovaries (g) GEN AN (AUTO) | Pituitary (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) | Uterus (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 0.0932 [1] | 0.0157 [1] | 0.6105 [2] | 0.3409 [1] | 0.0198 [2] | 0.4636 [2] |
| 0 | SD | 0.01167 | 0.00119 | 0.08380 | 0.07649 | 0.00386 | 0.05347 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 7 |
| Group 3 | Mean | 0.1044 | 0.0157 | 0.5882 | 0.2820 | 0.0178 | 0.5546 |
| 1.5 | SD | 0.01477 | 0.00243 | 0.04199 | 0.08047 | 0.00590 | 0.14427 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 6 |
| Group 4 | Mean | 0.1036 | 0.0153 | 0.6623 | 0.2928 | 0.0188 | 0.5272 |
| 10 | SD | 0.01724 | 0.00207 | 0.08273 | 0.05628 | 0.00207 | 0.04859 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 9 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]

GROUP 2: Control ZM
GROUPS 5 and 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 14:34:57

Day(s) Relative to Start Date

Sex: Male

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 2 | Mean | 485 [1] | 0.0808 [1] | 2.2158 [1] | 1.6787 [1] | 2.8997 [2] | 12.6467 [1] | 1.9413 [2] |
| 0 | SD | 33.5 | 0.01522 | 0.10137 | 0.20416 | 0.26177 | 1.14459 | 0.23674 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 5 | Mean | 493 | 0.0839 | 2.1536 | 1.6708 | 2.9014 | 13.0352 | 1.9180 |
| 1.5 | SD | 27.5 | 0.01426 | 0.06970 | 0.09339 | 0.17755 | 1.47132 | 0.11203 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 6 | Mean | 458 | 0.0877 | 2.2000 | 1.5988 | 3.0100 | 12.0322 | 1.9391 |
| 10 | SD | 59.6 | 0.02034 | 0.06686 | 0.19211 | 0.48504 | 2.06915 | 0.33262 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]

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TABLE 8a

GROUP 2: Control ZM
GROUPS 5 and 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 14:34:57

Day(s) Relative to Start Date

Sex: Male

| | | Pituitary (g) GEN AN (AUTO) | Prostate (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Testes (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 2 | Mean | 0.0150 R[1] | 1.0495 I[2] | 1.0669 R[1] | 3.6818 R[1] | 0.4265 L[2] | 0.0239 I[2] |
| 0 | SD | 0.00245 | 0.20279 | 0.23221 | 0.25437 | 0.08541 | 0.00250 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 5 | Mean | 0.0145 | 1.0625 | 1.0330 | 3.6587 | 0.5818 *[4] | 0.0228 |
| 1.5 | SD | 0.00143 | 0.13656 | 0.17428 | 0.27253 | 0.15341 | 0.00297 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 6 | Mean | 0.0155 | 0.9393 | 1.1399 | 3.2784 | 0.3999 | 0.0239 |
| 10 | SD | 0.00411 | 0.19528 | 0.61167 | 0.84029 | 0.11683 | 0.00419 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 |

[1][R - Automatic Transformation Selected: Rank]
[2][I - Automatic Transformation Selected: Identity (No Transformation)]
[3][L - Automatic Transformation Selected: Log]
[4] [* - Statistical Test: Dunnett 2 Sided p < 0.05]

TABLE 8a

GROUP 2: Control ZM
GROUPS 5 and 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 14:34:54

Day(s) Relative to Start Date

Sex: Female

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 2 | Mean | 284 I[2] | 0.0787 I[2] | 1.9865 I[2] | 0.9957 I[2] | 1.6563 I[2] | 8.0360 I[2] | 1.4001 L[3] |
| 0 | SD | 19.2 | 0.00970 | 0.09685 | 0.08783 | 0.11799 | 0.78485 | 0.15627 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 5 | Mean | 274 | 0.0786 | 2.0002 | 1.0435 | 1.6894 | 8.0023 | 1.4226 |
| 1.5 | SD | 22.1 | 0.00758 | 0.11703 | 0.10562 | 0.12559 | 0.86887 | 0.11703 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 6 | Mean | 278 | 0.0843 | 1.9836 | 1.0155 | 1.8078 | 7.9502 | 1.4178 |
| 10 | SD | 30.5 | 0.00919 | 0.07593 | 0.12011 | 0.20965 | 0.85108 | 0.15627 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[2][I - Automatic Transformation Selected: Identity (No Transformation)]
[3][L - Automatic Transformation Selected: Log]

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GROUP 2: Control ZM
GROUPS 5 and 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 14:34:54

Day(s) Relative to Start Date

Sex: Female

| | | Ovaries (g) GEN AN (AUTO) | Pituitary (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) | Uterus (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 2 | Mean | 0.0890 [1] | 0.0161 [1] | 0.7028 [2] | 0.3561 [2] | 0.0209 [1] | 0.4987 [2] |
| 0 | SD | 0.01337 | 0.00325 | 0.26496 | 0.06988 | 0.00284 | 0.06825 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 8 |
| Group 5 | Mean | 0.0985 | 0.0163 | 0.6519 | 0.3227 | 0.0199 | 0.5251 |
| 1.5 | SD | 0.01498 | 0.00197 | 0.10445 | 0.04166 | 0.00441 | 0.03130 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 8 |
| Group 6 | Mean | 0.0984 | 0.0160 | 0.7201 | 0.3515 | 0.0187 | 0.4848 |
| 10 | SD | 0.01871 | 0.00315 | 0.20406 | 0.10467 | 0.00605 | 0.03449 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 8 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]

GROUP 1: Control HS
GROUP 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:39:47

Day(s) Relative to Start Date

Sex: Male

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 1 | Mean | 541 [1] | 0.0652 [1] | 2.1460 [1] | 1.7415 [1] | 2.9594 [1] | 13.5106 [3] | 2.0242 [1] |
| 0 | SD | 56.9 | 0.01389 | 0.10899 | 0.15224 | 0.35457 | 1.88035 | 0.17938 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 4 | Mean | 578 | 0.0844 *,*[2] | 2.2287 | 1.8931 | 3.3106 | 14.4399 | 2.1371 |
| 10 | SD | 43.6 | 0.01206 | 0.09147 | 0.18148 | 0.24958 | 0.96300 | 0.21241 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2]["*" - Statistical Test: Dunnett 2 Sided p < 0.05,Statistical Test: T-Test Parametric 2 Sided p < 0.05]
[3][R - Automatic Transformation Selected: Rank]

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GROUP 1: Control HS
GROUP 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:39:47

Day(s) Relative to Start Date

Sex: Male

| | | Pituitary (g) GEN AN (AUTO) | Prostate (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Testes (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 1 | Mean | 0.0156 [1] | 1.2362 [1] | 1.0282 [1] | 3.5921 [1] | 0.3950 [2] | 0.0224 [1] |
| 0 | SD | 0.00240 | 0.14579 | 0.12804 | 0.26994 | 0.06210 | 0.00553 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 4 | Mean | 0.0167 | 1.1563 | 1.3175 | 3.6498 | 0.5793 [*,*2] | 0.0238 |
| 10 | SD | 0.00227 | 0.08336 | 0.34760 | 0.31137 | 0.11755 | 0.00451 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]
[*,*2][*,* - Statistical Test: Dunnett 2 Sided p < 0.05,Statistical Test: Wilcoxon 2 Sided p < 0.05]

GROUP 1: Control HS
GROUP 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:32:20

Day(s) Relative to Start Date

Sex: Female

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 1 | Mean | 286 [1] | 0.0741 [1] | 2.0280 [1] | 1.0902 [1] | 1.7296 [2] | 7.7880 [1] | 1.3469 [1] |
| 0 | SD | 27.7 | 0.00985 | 0.06354 | 0.15717 | 0.24179 | 0.78410 | 0.04411 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 4 | Mean | 297 | 0.0734 | 2.0692 | 1.1314 | 1.8491 | 7.8068 | 1.5003 [*,*2] |
| 10 | SD | 11.2 | 0.01656 | 0.08610 | 0.09783 | 0.07321 | 0.44832 | 0.10547 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][R - Automatic Transformation Selected: Rank]
[*,*2][*,* - Statistical Test: Dunnett 2 Sided p < 0.05,Statistical Test: T-Test Parametric 2 Sided p < 0.05]

GROUP 1: Control HS
GROUP 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 13:32:20

Day(s) Relative to Start Date

Sex: Female

| | | Ovaries (g) GEN AN (AUTO) | Pituitary (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) | Uterus (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 1 | Mean | 0.1052 [1] | 0.0169 [1] | 0.6401 [1] | 0.2682 [1] | 0.0204 [1] | 0.6012 [1] |
| 0 | SD | 0.03414 | 0.00294 | 0.10139 | 0.05108 | 0.00209 | 0.07411 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 4 | Mean | 0.0993 | 0.0174 | 0.6677 | 0.3047 | 0.0186 | 0.5798 |
| 10 | SD | 0.01042 | 0.00244 | 0.10330 | 0.10004 | 0.00317 | 0.07076 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]

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GROUP 2: Control ZM
GROUP 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 15:07:02

Day(s) Relative to Start Date

Sex: Male

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 2 | Mean | 547 [L1] | 0.0675 [I2] | 2.1803 [I2] | 1.8405 [I2] | 3.1397 [I2] | 14.6472 [I2] | 1.9174 [I2] |
| 0 | SD | 31.1 | 0.01427 | 0.07164 | 0.22617 | 0.28686 | 1.93203 | 0.19199 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 6 | Mean | 549 | 0.0800 | 2.2161 | 1.8061 | 3.3585 | 14.5056 | 2.1722 |
| 10 | SD | 66.4 | 0.00841 | 0.08065 | 0.17128 | 0.46373 | 1.64933 | 0.26392 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[1][L - Automatic Transformation Selected: Log]
[2][I - Automatic Transformation Selected: Identity (No Transformation)]

GROUP 2: Control ZM
GROUP 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 15:07:02

Day(s) Relative to Start Date

Sex: Male

| | | Pituitary (g) GEN AN (AUTO) | Prostate (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Testes (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 2 | Mean | 0.0161 [I1] | 1.3499 [I1] | 1.0272 [I1] | 3.5782 [I1] | 0.4178 [I1] | 0.0225 [I1] |
| 0 | SD | 0.00265 | 0.16374 | 0.07685 | 0.49919 | 0.11364 | 0.00327 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 6 | Mean | 0.0148 | 1.3862 | 1.0388 | 3.5591 | 0.4609 | 0.0255 |
| 10 | SD | 0.00113 | 0.14606 | 0.14960 | 0.25930 | 0.13554 | 0.00355 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]

GROUP 2: Control ZM
GROUP 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 15:07:06

Day(s) Relative to Start Date

Sex: Female

| | | Terminal BW (g) GEN AN (AUTO) | Adrenals (g) GEN AN (AUTO) | Brain (g) GEN AN (AUTO) | Heart (g) GEN AN (AUTO) | Kidneys (g) GEN AN (AUTO) | Liver (g) GEN AN (AUTO) | Lungs Trachea (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 2 | Mean | 285 [R1] | 0.0651 [I2] | 1.9865 [R1] | 1.0439 [R1] | 1.5975 [I2] | 7.5661 [R1] | 1.3609 [I2] |
| 0 | SD | 9.4 | 0.00750 | 0.05497 | 0.00876 | 0.21139 | 0.41799 | 0.10947 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 6 | Mean | 295 | 0.0735 | 1.9999 | 1.1209 | 1.7775 | 7.9837 | 1.3995 |
| 10 | SD | 20.3 | 0.00454 | 0.05715 | 0.07275 | 0.11899 | 0.87364 | 0.06519 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[1][R - Automatic Transformation Selected: Rank]
[2][I - Automatic Transformation Selected: Identity (No Transformation)]



Reference ID: 3028604

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GROUP 2: Control ZM
GROUP 6: Zemplar®

71332 - ORGAN WEIGHTS - ABSOLUTE
SUMMARY OF MEANS

11/03/2011 15:07:06

Day(s) Relative to Start Date

Sex: Female

| | | Ovaries (g) GEN AN (AUTO) | Pituitary (g) GEN AN (AUTO) | Spleen (g) GEN AN (AUTO) | Thymus (g) GEN AN (AUTO) | Thyroid Parathy (g) GEN AN (AUTO) | Uterus (g) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|
| | | 42 | 42 | 42 | 42 | 42 | 42 |
| Group 2 | Mean | 0.1104 I[a] | 0.0180 I[a] | 0.6155 I[a] | 0.3322 I[a] | 0.0212 I[a] | 0.5449 I[a] |
| 0 | SD | 0.03825 | 0.00429 | 0.08878 | 0.10157 | 0.00327 | 0.08010 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 6 | Mean | 0.0925 | 0.0164 | 0.5900 | 0.4066 | 0.0187 | 0.5322 |
| 10 | SD | 0.01091 | 0.00441 | 0.12588 | 0.07572 | 0.00249 | 0.07908 |
| µg/kg/dose | N | 5 | 5 | 5 | 5 | 5 | 5 |

[a][I - Automatic Transformation Selected: Identity (No Transformation)]

GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - RELATIVE TO TERMINAL BODY WEIGHT
SUMMARY OF MEANS

11/03/2011 13:20:24

Day(s) Relative to Start Date

Sex: Male

| | | Adrenals BW (%) GEN AN (AUTO) | Brain BW (%) GEN AN (AUTO) | Heart BW (%) GEN AN (AUTO) | Kidneys BW (%) GEN AN (AUTO) | Liver BW (%) GEN AN (AUTO) | Lungs Trachea BW (%) GEN AN (AUTO) | Pituitary BW (%) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 0.0145 I[a] | 0.4442 R[b] | 0.3298 I[a] | 0.5875 R[b] | 2.5953 I[a] | 0.3880 I[a] | 0.0028 L[c] |
| 0 | SD | 0.00253 | 0.07311 | 0.02462 | 0.05238 | 0.10567 | 0.04879 | 0.00025 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 3 | Mean | 0.0160 | 0.4416 | 0.3321 | 0.5857 | 2.5497 | 0.3964 | 0.0032 |
| 1.5 | SD | 0.00178 | 0.04763 | 0.01902 | 0.03084 | 0.14116 | 0.03538 | 0.00060 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 4 | Mean | 0.0207 ***[a] | 0.4523 | 0.3351 | 0.6362 | 2.7047 | 0.4066 | 0.0030 |
| 10 | SD | 0.00356 | 0.05268 | 0.01561 | 0.06953 | 0.16573 | 0.03055 | 0.00036 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[a][I - Automatic Transformation Selected: Identity (No Transformation)]
[a]*** - Statistical Test: Dunnett 2 Sided p < 0.001]
[b][R - Automatic Transformation Selected: Rank]
[c] [L - Automatic Transformation Selected: Log]

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GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - RELATIVE TO TERMINAL BODY WEIGHT
SUMMARY OF MEANS

11/03/2011 13:20:24

Day(s) Relative to Start Date

Sex: Male

| | | Prostate BW (%) GEN AN (AUTO) | Spleen BW (%) GEN AN (AUTO) | Testes BW (%) GEN AN (AUTO) | Thymus BW (%) GEN AN (AUTO) | Thyroid Parathy BW (%) GEN AN (AUTO) |
|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 0.2150 I[1] | 0.2301 L[2] | 0.7493 L[2] | 0.0957 L[2] | 0.0048 I[1] |
| 0 | SD | 0.03425 | 0.05784 | 0.06716 | 0.02346 | 0.00074 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 |
| Group 3 | Mean | 0.2199 | 0.2156 | 0.7246 | 0.0931 | 0.0050 |
| 1.5 | SD | 0.02926 | 0.02169 | 0.10697 | 0.02674 | 0.00062 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 |
| Group 4 | Mean | 0.2299 | 0.2133 | 0.8103 | 0.0820 | 0.0050 |
| 10 | SD | 0.03496 | 0.02854 | 0.09246 | 0.01895 | 0.00096 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][L - Automatic Transformation Selected: Log]

GROUP 1: Control HS
GROUPS 3 and 4: Paricalcitol Hospira

71332 - ORGAN WEIGHTS - RELATIVE TO TERMINAL BODY WEIGHT
SUMMARY OF MEANS

11/03/2011 13:13:46

Day(s) Relative to Start Date

Sex: Female

| | | Adrenals BW (%) GEN AN (AUTO) | Brain BW (%) GEN AN (AUTO) | Heart BW (%) GEN AN (AUTO) | Kidneys BW (%) GEN AN (AUTO) | Liver BW (%) GEN AN (AUTO) | Lungs Trachea BW (%) GEN AN (AUTO) | Ovaries BW (%) GEN AN (AUTO) |
|---|---|---|---|---|---|---|---|---|
| | | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Group 1 | Mean | 0.0265 I[1] | 0.7360 I[1] | 0.3771 R[3] | 0.6044 I[1] | 2.7864 I[1] | 0.4992 I[1] | 0.0343 I[1] |
| 0 | SD | 0.00276 | 0.03875 | 0.02632 | 0.04398 | 0.14286 | 0.02925 | 0.00387 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 3 | Mean | 0.0276 | 0.7297 | 0.3695 | 0.6020 | 2.8292 | 0.5004 | 0.0379 |
| 1.5 | SD | 0.00410 | 0.06008 | 0.02872 | 0.04310 | 0.14775 | 0.03494 | 0.00448 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group 4 | Mean | 0.0319 **[2] | 0.7540 | 0.3790 | 0.6845 **[2] | 2.9746 ** | 0.5302 | 0.0393 |
| 10 | SD | 0.00437 | 0.06052 | 0.00928 | 0.05439 | 0.20629 | 0.03871 | 0.00738 |
| µg/kg/dose | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[1][I - Automatic Transformation Selected: Identity (No Transformation)]
[2][** - Statistical Test: Dunnett 2 Sided p < 0.01]
[3][R - Automatic Transformation Selected: Rank]
* [* - Statistical Test: Dunnett 2 Sided p < 0.05]

## Gross Pathology:

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APPENDIX 11

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| ADRENALS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 9 | 10 | 10 | 10 | 10 | 10 |
| Small | 1 | 0 | 0 | 0 | 0 | 0 |
| AORTA: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| BRAIN: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| CECUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 |
| Displacement | 0 | 0 | 0 | 0 | 0 | 1 |
| COLON: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| DUODENUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| JEJUNUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| ILEUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LIVER: (continued) | | | | | | |
| Adhesion | 1 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 0 | 0 | 0 | 0 | 0 | 0 |
| LN, BRONCHIAL: | | | | | | |
| Submitted | (1) | (3) | (2) | (2) | (2) | (3) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 1 | 3 | 2 | 2 | 2 | 3 |
| LN, ILIAC: | | | | | | |
| Submitted | (1) | (0) | (1) | (0) | (1) | (3) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark discoloration | 0 | 0 | 1 | 0 | 0 | 0 |
| Enlargement | 1 | 0 | 1 | 0 | 1 | 3 |
| LN, MANDIBULAR: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 10 | 9 | 9 |
| Dark discoloration | 0 | 0 | 0 | 0 | 0 | 1 |
| Dark focus | 0 | 0 | 1 | 0 | 1 | 0 |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 0 |
| LN, MEDIASTINAL: | | | | | | |
| Submitted | (0) | (0) | (2) | (2) | (2) | (0) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 0 | 0 | 1 | 0 | 0 | 0 |
| Dark discoloration | 0 | 0 | 1 | 1 | 1 | 0 |
| Enlargement | 0 | 0 | 1 | 1 | 1 | 0 |
| LN, MESENTERIC: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| LN, PANCREATIC: | | | | | | |
| Submitted | (0) | (0) | (0) | (0) | (0) | (1) |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

| Removal Reason: Terminal | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, PANCREATIC; (continued) | | | | | | |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark focus | 0 | 0 | 0 | 0 | 0 | 1 |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 1 |
| LN, RENAL; | | | | | | |
| Submitted | (0) | (0) | (0) | (0) | (0) | (0) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 0 |
| LUNGS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 8 | 9 | 9 | 9 | 8 | 10 |
| Dark focus | 2 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 1 | 1 | 1 | 1 | 2 | 0 |
| Pale area | 0 | 0 | 0 | 0 | 0 | 0 |
| MAMMARY GLAND; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| OPTIC NERVES; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| OVARIES; | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| PANCREAS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PARATHYROIDS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| PARATHYROIDS: (continued) | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PITUITARY: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PROSTATE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| RECTUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SG, MANDIBULAR: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 9 | 10 | 10 | 10 | 10 | 10 |
| Gelatinous material | 1 | 0 | 0 | 0 | 0 | 0 |
| SCIATIC NERVE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SEMINAL VESICLES: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SKELETAL MUSCLE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SKIN & SUBCUTIS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| SC. CERVICAL: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SPLEEN: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 1 |
| Pale area | 0 | 0 | 0 | 0 | 0 | 0 |
| STERNUM & MARROW: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| STOMACH: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 10 | 9 | 10 |
| Dark focus | 0 | 0 | 1 | 0 | 0 | 0 |
| Depressed area | 0 | 0 | 0 | 0 | 1 | 0 |
| TESTES: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 |
| Small | 0 | 0 | 0 | 0 | 0 | 1 |
| THYMUS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 8 | 10 | 8 | 8 | 6 | 7 |
| Dark area | 0 | 0 | 1 | 1 | 2 | 1 |
| Dark focus | 0 | 0 | 0 | 1 | 1 | 0 |
| Mottled | 2 | 0 | 2 | 0 | 2 | 2 |
| THYROID GLAND: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | MALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| THYROID GLAND; (continued) | | | | | | |
| Aplasia (not found) | 0 | 0 | 0 | 0 | 0 | 0 |
| TONGUE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| TRACHEA: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| URINARY BLADDER: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| UTERUS: | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| VAGINA: | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| INFUSION SITE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 3 | 3 | 6 | 3 | 4 | 0 |
| Dark material | 0 | 2 | 0 | 1 | 1 | 1 |
| Gelatinous material | 0 | 0 | 0 | 0 | 0 | 1 |
| Pale material | 7 | 4 | 4 | 6 | 6 | 9 |
| Thickening | 1 | 1 | 0 | 0 | 0 | 1 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| ADRENALS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| Small | 0 | 0 | 0 | 0 | 0 | 0 |
| AORTA: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| BRAIN: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| CECUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| Displacement | 0 | 0 | 0 | 0 | 0 | 0 |
| COLON: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| DUODENUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| JEJUNUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| ILEUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:4

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| EPIDIDYMIDES: | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| Small | - | - | - | - | - | - |
| ESOPHAGUS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| EYES: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| FEMUR & MARROW: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| HEART: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| KIDNEYS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 9 | 8 | 9 | 10 |
| Adhesion | 0 | 1 | 0 | 1 | 0 | 0 |
| Depressed area | 0 | 0 | 0 | 0 | 0 | 0 |
| Dilation, pelvis | 0 | 0 | 0 | 0 | 1 | 0 |
| Mottled | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale area | 0 | 0 | 1 | 1 | 0 | 0 |
| Pale discoloration | 0 | 0 | 0 | 0 | 0 | 0 |
| Irregular surface | 0 | 0 | 0 | 0 | 0 | 0 |
| LIVER: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 9 | 10 | 10 | 10 | 10 | 10 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:49

| Removal Reason: Terminal | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LIVER; (continued) | | | | | | |
| Adhesion | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 1 | 0 | 0 | 0 | 0 | 0 |
| LN, BRONCHIAL; | | | | | | |
| Submitted | (0) | (1) | (1) | (0) | (0) | (1) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 1 | 1 | 0 | 0 | 1 |
| LN, ILIAC; | | | | | | |
| Submitted | (2) | (0) | (0) | (0) | (0) | (1) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark discoloration | 1 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 1 | 0 | 0 | 0 | 0 | 1 |
| LN, MANDIBULAR; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 7 | 9 | 10 | 9 |
| Dark discoloration | 0 | 0 | 1 | 0 | 0 | 0 |
| Dark focus | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 1 | 3 | 1 | 0 | 1 |
| LN, MEDIASTINAL; | | | | | | |
| Submitted | (0) | (0) | (1) | (2) | (0) | (3) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark discoloration | 0 | 0 | 0 | 1 | 0 | 0 |
| Enlargement | 0 | 0 | 1 | 1 | 0 | 3 |
| LN, MESENTERIC; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| LN, PANCREATIC; | | | | | | |
| Submitted | (0) | (0) | (0) | (0) | (0) | (1) |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| LN, PANCREATIC; (continued) | | | | | | |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark focus | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 1 |
| LN, RENAL; | | | | | | |
| Submitted | (0) | (1) | (0) | (0) | (0) | (1) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 1 | 0 | 0 | 0 | 1 |
| LUNGS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 9 | 10 |
| Dark focus | 0 | 0 | 0 | 0 | 0 | 0 |
| Dark area | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale area | 0 | 0 | 0 | 0 | 1 | 0 |
| MAMMARY GLAND; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| OPTIC NERVES; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| OVARIES; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PANCREAS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PARATHYROIDS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:48

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| PARATHYROIDS: (continued) | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PITUITARY: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| PROSTATE: | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| RECTUM: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SG, MANDIBULAR: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| Gelatinous material | 0 | 0 | 0 | 0 | 0 | 0 |
| SCIATIC NERVE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SEMINAL VESICLES: | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| SKELETAL MUSCLE: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SKIN & SUBCUTIS: | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 09/02/11 11:48

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| SC, CERVICAL; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| SPLEEN; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 10 | 9 | 10 | 10 |
| Enlargement | 0 | 1 | 0 | 0 | 0 | 0 |
| Pale area | 0 | 0 | 0 | 1 | 0 | 0 |
| STERNUM & MARROW; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| STOMACH; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| Dark focus | 0 | 0 | 0 | 0 | 0 | 0 |
| Depressed area | 0 | 0 | 0 | 0 | 0 | 0 |
| TESTES; | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (-) | (-) |
| No Visible Lesions | - | - | - | - | - | - |
| Small | - | - | - | - | - | - |
| THYMUS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 8 | 7 | 9 | 9 | 10 | 9 |
| Dark area | 0 | 2 | 0 | 1 | 0 | 0 |
| Dark focus | 0 | 1 | 0 | 0 | 0 | 0 |
| Mottled | 2 | 1 | 1 | 0 | 0 | 1 |
| THYROID GLAND; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 11:4

Removal Reason: Terminal

| | FEMALES | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| | 0 | 0 | 1.5 | 10 | 1.5 | 10 |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (10) |
| THYROID GLAND; (continued) | | | | | | |
| Aplasia (not found) | 0 | 0 | 0 | 0 | 0 | 1 |
| TONGUE; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| TRACHEA; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| URINARY BLADDER; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| UTERUS; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| VAGINA; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 |
| INFUSION SITE; | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (10) |
| No Visible Lesions | 7 | 6 | 6 | 3 | 5 | 2 |
| Dark material | 2 | 0 | 0 | 0 | 0 | 1 |
| Gelatinous material | 0 | 0 | 0 | 0 | 0 | 0 |
| Pale material | 1 | 3 | 4 | 7 | 5 | 5 |
| Thickening | 0 | 1 | 0 | 0 | 0 | 2 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 09/02/11 11:4

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| ADRENALS: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Small | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| AORTA: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 3 | 5 | 5 | 5 | 5 | 5 |
| Irregular surface | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| BRAIN: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| CECUM: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| COLON: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| DUODENUM: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| JEJUNUM: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Diverticulum | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| ILEUM: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:4

| Removal Reason: Recovery | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| EPIDIDYMIDES; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5 | 4 | 5 | 5 | - | - | - | - |
| Small | 0 | 1 | 0 | 0 | - | - | - | - |
| ESOPHAGUS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| EYES; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| FEMUR & MARROW; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| HEART; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| KIDNEYS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 4 | 3 | 4 | 5 | 5 | 4 | 5 |
| Depressed area | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Dilation, pelvis | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Pale discoloration | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Irregular surface | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 |
| Enlargement | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Firm | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Mottled | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

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GROUP 1: Control HS
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GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 08/02/11 11:46

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| LIVER: (continued) | | | | | | | | |
| Raised area | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LN, BRONCHIAL: | | | | | | | | |
| Submitted | (0) | (0) | (1) | (1) | (0) | (0) | (1) | (0) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 |
| LN, ILIAC: | | | | | | | | |
| Submitted | (0) | (0) | (2) | (1) | (0) | (1) | (1) | (0) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 0 | 2 | 1 | 0 | 1 | 1 | 0 |
| LN, MANDIBULAR: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 4 |
| Enlargement | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| LN, MESENTERIC: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| LN, PANCREATIC: | | | | | | | | |
| Submitted | (0) | (1) | (2) | (0) | (0) | (0) | (0) | (1) |
| No Visible Lesions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enlargement | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 1 |
| LUNGS: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 4 | 4 | 5 | 5 | 5 | 4 |
| Dark area | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Pale area | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| MAMMARY GLAND: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

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Date: 08/02/11 11:45

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| MAMMARY GLAND; (continued) | | | | | | | | |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| OPTIC NERVES; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| OVARIES; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (5) | (5) | (5) | (5) |
| No Visible Lesions | - | - | - | - | 5 | 5 | 5 | 5 |
| PANCREAS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mottled | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| PARATHYROIDS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| PITUITARY; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| PROSTATE; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5 | 5 | 5 | 5 | - | - | - | - |
| RECTUM; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| SG, MANDIBULAR; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:45

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| SCIATIC NERVE; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| SEMINAL VESICLES; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5 | 5 | 5 | 5 | - | - | - | - |
| SKELETAL MUSCLE; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| SKIN & SUBCUTIS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| SC, CERVICAL; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| SPLEEN; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 3 | 5 | 5 | 5 | 5 | 5 |
| Enlargement | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| STERNUM & MARROW; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| STOMACH; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 3 | 4 | 5 | 5 | 5 | 5 |
| Thickening | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 |

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GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:45

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| TESTES; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5 | 4 | 5 | 5 | - | - | - | - |
| Small | 0 | 1 | 0 | 0 | - | - | - | - |
| Soft | 0 | 1 | 0 | 0 | - | - | - | - |
| THYMUS; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 4 | 4 | 3 | 5 | 5 | 5 | 5 |
| Dark area | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Dark focus | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| THYROID GLAND; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| TONGUE; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| TRACHEA; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| URINARY BLADDER; | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| UTERUS; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (5) | (5) | (5) | (5) |
| No Visible Lesions | - | - | - | - | 5 | 5 | 5 | 5 |
| VAGINA; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (5) | (5) | (5) | (5) |
| No Visible Lesions | - | - | - | - | 5 | 5 | 5 | 5 |

GROUP 1: Control HS
GROUP 2: Control ZM
GROUPS 3 and 4: Paricalcitol Hospira
GROUPS 5 and 6: Zemplar®

71332 - INCIDENCE OF GROSS PATHOLOGY

Date: 08/02/11 11:45

Removal Reason: Recovery

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 4 | Group 6 | Group 1 | Group 2 | Group 4 | Group 6 |
| | 0 | 0 | 10 | 10 | 0 | 0 | 10 | 10 |
| Number of Animals on Study : | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Number of Animals Completed: | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| INFUSION SITE: | | | | | | | | |
| Submitted | (5) | (5) | (5) | (5) | (5) | (5) | (5) | (5) |
| No Visible Lesions | 4 | 2 | 0 | 1 | 3 | 2 | 3 | 3 |
| Dark material | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 |
| Pale material | 1 | 3 | 4 | 3 | 2 | 3 | 1 | 2 |
| Thickening | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |

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/s/

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PARVANEH ESPANDIARI
10/13/2011

KAREN L DAVIS BRUNO
10/13/2011
see Pharm/Tox TL memo also

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 201657 **Applicant:** Hospira, Inc. **Stamp Date:** 07 April 2011

**Drug Name:** Paricalcitol Injection, 2 mcg/m and 5mcg/mL **NDA Type:** 505(b)2 **Indication:** Prevention and treatment of secondary hyperparathyrodism associated with chronic kidney disease Stage 5

| | Content Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin? | X | | Section 4.2.3. Toxicology |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin? | X | | |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin? | X | | |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)? | | | Due to different concentrations of (b) (4) propylene glycol in the RLD, Zemplar®, and in the new product, Hospira Paricalcitol, a bridging 4-week repeat dose intravenous (bolus) toxicity study with the 2-week recovery period in SD rats was conducted. |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | | | The repeat-dose toxicity study was conducted with: the appropriate route of administration (intravenous bolus injection via a surgically implanted intravenous catheter); and the same formulation that the new product will be marketed. |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route? | X | | |
| 7 | Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? | X | | |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | ___ | ___ | Not Applicable |

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 9 | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | X | | The proposed labeling is the same as the labeling of the RLD and data express human dose multiples in $mg/m^2$. |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.) | | X | |
| 11 | Has the applicant addressed any abuse potential issues in the submission? | | X | |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted? | X | | Provided a nonclinical toxicity bridge study to the RLD is sufficient. |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____**Yes_√___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Parvaneh Espandiari, Ph.D

Reviewing Pharmacologist Date

Karen Davis-Bruno, Ph.D

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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PARVANEH ESPANDIARI
05/09/2011

KAREN L DAVIS BRUNO
05/09/2011
P/T filing memo