SAFETY EVALUATION OF UNIVESTIN®

CONFIDENTIAL

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Safety Evaluation of Univestin®

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1.0 INTRODUCTION

Intertek Scientific & Regulatory Consultancy (Intertek) was requested by Unigen to conduct a comprehensive evaluation of the available safety data for Univestin®. Univestin® products, sold as dietary supplements, contain the ingredients baicalin and catechins, derived from *Scutellaria baicalensis* (*S. baicalensis*) and *Acacia catechu (A. catechu)*, respectively. Univestin® has been sold successfully for over 15 years. Based on sales figures provided by Unigen, it has been sold in over 14 countries spanning the globe and has been consumed in more than 5.7 billion doses (125 mg) during this time period.

On this basis, Intertek evaluated the product-specific safety studies conducted with Univestin® that assessed general toxicity as well as developmental and reproductive effects in rats and rabbits, while focusing closely on those parameters associated with potential effects on the liver or lung as such effects were highlighted by the United States (U.S.) Food and Drug Administration (FDA) as a concern associated with 1 related medical food product. In addition, Intertek conducted a comprehensive search of the scientific literature to identify any non-clinical and clinical studies that reported adverse effects associated with Univestin® or its ingredients, in particular hypersensitivity pneumonitis and drug-induced liver injury. A summary of the available safety studies and case reports of adverse events associated with Univestin® is presented herein.

2.0 PRODUCT INFORMATION

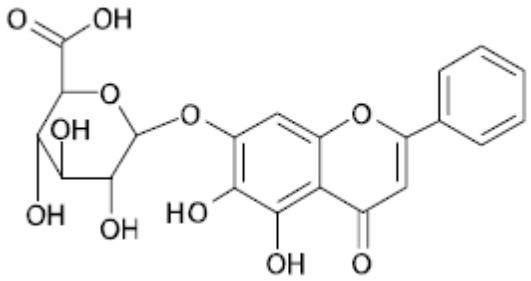
2.1 Overview

Univestin®, also known as UP446, is a proprietary blend of 2 flavonoids: baicalin, derived from the roots of *S. baicalensis*, and catechin, obtained from the bark and heartwood of *A. catechu.* It is prepared by a 70% ethanol and subsequent aqueous extraction and further purified by recrystallization (Tseng-Crank *et al*., 2010). Univestin® supplements are typically used at dosages of 250 mg/day, with some users consuming up to 500 mg/day.

2.1.1 Baicalin

Baicalin (5,6,7-trihydroxyflavone,7-O-β-D-glucuronopyranoside) is derived from the roots of *S. baicalensis*. Georgi (family Lamiaceae), also known as Chinese skullcap. The molecular weight of baicalin is 446.37 and its molecular formula is $C_{21}H_{18}O_{11}$. Its chemical structure is shown in Figure 2.1.1-1.

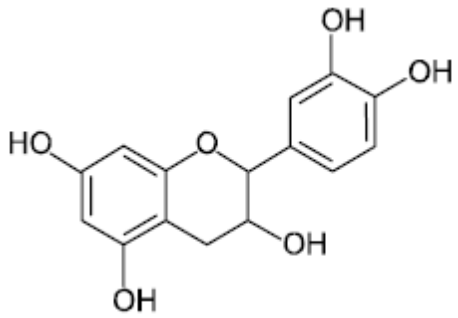
Figure 2.1.1-1 Chemical Structure of Baicalin



2.1.2 Catechin

Catechin (3,3',4',5,7-pentahydroxyflavan [2R,3S form]) and its stereo-isomer, epicatechin (3,3',4',5,7-pentahydroxyflavan [2R,3R form]), are derived from the bark and heartwood of *A. catechu* (family Mimosaceae). It has a molecular weight of 290.27. Its molecular formula is $C_{15}H_{14}O_6$. The chemical structure is shown in Figure 2.1.2-1.

Figure 2.1.2-1 Chemical Structure of Catechin



2.2 Chemical Composition

Univestin® (UP446) is comprised of *S. baicalensis* extract (≥75%), *A. catechu* extract (≥65%), and United States Pharmacopeia (USP) maltodextrin at a ratio of approximately 80:17:3. An analysis of the chemical composition of UP446 was performed by high-performance liquid chromatography (HPLC) in Yimam *et al.* (2010) and Burnett *et al*. (2007a). The chemical composition of UP446, as analyzed in these studies, is described alongside a second lot of UP446 in Table 2.2-1.

Table 2.2-1 Chemical Composition of Univestin® (UP446)

Active Compounds	Composition (%)	
	UP446 (Burnett *et al*., 2007a; Yimam *et al*., 2010)	**UP446 (Lot UVG17002)[a]**
S. baicalensis extract		
Baicalin	62.5	66
Wogon-7-glucuronide	6.7	--
Oroxylin A 7-glucuronide	2	--
Baicalein	1.5	--
Wogonin	1.1	--
Chrysin-7-glucuronide	0.8	--
5-Methyl-wogonin-7-glucuronide	0.5	--
Scutellarin	0.3	--
Norwogonin	0.3	--
Chrysin	<0.2	--
Oroxylin A	<0.2	--
Total free-B-ring flavonoids	75.7±10	66
A. catechu extract		
Catechin	9.9	16
Epicatechin	0.4	--
Total flavans	10.3±10	16
Total active ingredients[b]	86±10	82

A. catechu = Acacia catechu; S. baicalensis = Scutellaria baicalensis.
[a] Only percentage of baicalin and catechin described.
[b] The UP446 combination, standardized extract also contained approximately 3% unidentified content, 5% moisture, and 6% added excipient (maltodextrin) to control flow characteristics of the final composition in the powdered form. Each component in the mixture varied by not more than 10%.

2.3 Product Specifications and Batch Analysis

Product specifications and analysis of 1 representative batch of Univestin® are provided in Table 2.3-1.

Table 2.3-1 Summary of Product Specifications and Example Product Analysis for Univestin®

Specification Parameter	Method	Specification	Manufacturing Lot
			UVG17002
Color and Appearance	Organoleptic	Greenish yellow to brown powder	Conforms
Loss on Drying	105°C, 2 hours	NMT 5.0%	3.0%
Identification	HPLC	Match HPLC chromatographic profile	Match
Assay Free-b-ring flavonoid (baicalin) Flavans (catechins)	HPLC	NLT 60% NLT 10%	66% 16%
Particle size	RQ-TAP	NLT 80% pass – 80 mesh	90%

Table 2.3-1 Summary of Product Specifications and Example Product Analysis for Univestin®

Specification Parameter	Method	Specification	Manufacturing Lot
			UVG17002
Heavy Metals			
Lead	ICP-OES	NMT 0.5 ppm	0.3 ppm
Cadmium		NMT 1.5 ppm	< 0.1 ppm
Mercury		NMT 1.0 ppm	< 0.1 ppm
Arsenic		NMT 1.0 ppm	0.6 ppm
Pesticide residues		USP limits	Not detected
Alfatoxins total B1, B2, G1, & G2	KFDA	NMT 20 ppb	Not detected
Aflatoxin B1	KFDA	NMT 5 ppb	Not detected
Microorganisms			
Total aerobic plate count	KFDA	NMT 10,000 cfu/g	<10 cfu/g
Mold and yeast		NMT 100 cfu/g	<10 cfu/g
Staphylococcus aureus		Absent	Not detected
E. coli		Absent	Not detected
Salmonella spp.		Absent	Not detected
Enterobacteria	USP	NMT 100 cfu/g	Not detected

cfu = colony-forming units; HPLC = high-performance liquid chromatography; ICP-OES = inductively coupled plasma-optical emission spectrometry; KFDA = Korean Food and Drug Administration; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia.

2.4 Mechanism of Action

Univestin® is a dietary supplement marketed to support joint health. Joint stiffness and discomfort may be related to thinning of cartilage, ultimately resulting in osteoarthritis (OA). On a biochemical level, OA involves accelerated metabolism of arachidonic acid (AA) generated from cell membranes by the action of phospholipase A. AA is metabolized by parallel pathways, cyclooxygenase and 5-lipoxygenase, (5-LOX) with each producing inflammatory compounds, including prostaglandins and leukotrienes. Many OA treatments work *via* inhibition of cyclooxygenase (COX-1, COX-2) pathways, resulting in reduction of inflammatory mediators such as prostaglandins and prostacyclins. However, this shunts arachidonic metabolism down the 5-LOX path with a resultant increase in levels of highly chemotactic and inflammatory leukotrienes which can result in toxicity. Dual pathway inhibitors block all 3 of the primary AA metabolic pathways and seem to have less cardiovascular gastrointestinal side effects than commonly used OA drugs (*i.e.,* nonsteroidal anti-inflammatory drugs or selective COX-2 inhibitors) (Burnett *et al.*, 2007b; Sampalis and Brownell, 2012).

The blend of baicalin and catechin has demonstrated clinical efficacy against OA and preclinical efficacy in an animal model of rheumatoid arthritis (Burnett *et al.*, 2007b; Arjmandi *et al.*, 2014; Sampalis and Brownell, 2012; Yimam *et al.,* 2013). It also shows anti-inflammatory, antioxidant and analgesic activity in experimental animal models (Yimam *et al.*, 2012, 2013).

3.0 SUMMARY OF AVAILABLE SAFETY DATA

A series of safety studies have been conducted in rats, mice, and dogs to assess general toxicity following acute, subchronic, and chronic exposure to Univestin® (identified as UP446 in the publications). In addition, the potential effects of UP446 on developmental and reproductive endpoints have been evaluated in in rats and rabbits. Furthermore, clinical studies have evaluated the safety and efficacy of UP446 in subjects with OA.

3.1 Non-Clinical Studies

3.1.1 Acute Toxicity Studies

In a study adhering to Organization for Economic Co-operation and Development (OECD) Guideline 425 and Good Laboratory Practice (GLP) (OECD, 1998, 2008), 10 male and 10 female Sprague-Dawley rats were split evenly in 2 groups and fed *via* oral gavage either 0 or 5,000 mg UP446/kg body weight in a single oral dose (Lee *et al.,* 2013). Carboxymethylcellulose sodium salt (0.5%) in water was used as the vehicle and control. The rats were monitored for mortality, clinical signs, body weight change, and gross findings for 14 days following treatment. No treatment-related adverse effects were reported in the 14 days following the administration of UP446, including weight changes and gross pathology. The authors concluded that the acute lethal dose of UP446 to be greater than the tested dose of 5,000 mg/kg body weight under the conditions of this study (Lee *et al.,* 2013).

In a study by Burnett *et al.* (2007a), groups of 10 male and 10 female ICR mice were randomly assigned to receive either 0 (water) or 2,000 mg/kg body weight/day of UP446 suspended in deionized water *via* oral gavage for 14 consecutive days. Animals were housed 5 per cage and maintained with a 12-hour light/dark cycle. Food and water were available *ad libitum*. Clinical and behavioral signs were observed once daily. Body weight and food and water consumption were measured and recorded once a week. After the completion of the treatment period, the mice were killed with isoflurane and subject to gross necropsy. Blood was collected and analyzed for red blood cell count, white blood cell count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and platelet count. Serum parameters included total protein, albumin, globulin, total bilirubin, total cholesterol, total glucose, blood urea nitrogen, creatine, phosphorus, sodium, chloride, potassium, calcium, alanine phosphatase, and alanine aminotransferase. The liver, kidney, duodenum, and stomach were removed and examined for histological changes, and all tissues and organs were observed for macroscopic changes. No deaths or effects on body weight were reported during the treatment. Red blood cell count was reported to fall below the reference range in male treated mice. Similarly, mean cell volume and platelet count was below the reference range in female treated mice. For plasma biochemistry parameters, liver alanine aminotransferase levels were reported to be above the reference range in treated males only. Statistics on these findings were not reported. No other treatment-related effects were reported from this study (Burnett *et al.,* 2007a).

In a study by Yimam *et al.* (2016a), 16 male beagle dogs were split into 4 groups and treated with 0, 250, 500, or 1,000 mg UP446/kg body weight/day in 0.5% carboxymethylcellulose sodium salt solution with water *via* oral gavage with ascending doses. The study was conducted in compliance with the OECD GLP (OECD, 1998). The evaluated endpoints were cardiovascular system effects. The authors reported vomiting in 1 control and 1 animal at 500 mg/kg. However, there was no statistically significant or biologically relevant change in blood pressure, heart rate, or electrocardiogram parameters. The authors also performed 2 studies with male rats split into 4 groups consisting of 6 to 8 rats per group. Animals were treated with 0, 800, 2,000, or 5,000 mg UP446/kg body weight in 0.5% carboxymethylcellulose sodium salt solution with water *via* oral gavage. The rats were observed for 24 hours post dosing. One rat study evaluated central nervous system endpoints and only found an increase in forelimb strength 1-hour post dose in the rats treated with 800 mg UP446/kg body weight, and an increase in fecal pellets 9-hours post dose in the rats treated with 2,000 mg UP446/kg body weight, and 24 hours post-dose in the rats treated with 2,000 and 5,000 mg UP446/kg body weight/day. No other statistically significant effects on the central nervous system were found. The other rat study evaluated respiratory endpoints and found no statistically significant or biologically relevant changes in respiratory rate, tidal volume, or minute volume when compared to the control, prior to or up to 24 hours after dosing. The authors conclude that the data suggests that UP446 has no adverse effect on the respiratory, cardiovascular, and central nervous systems.

3.1.2 Repeat Dose Toxicity Studies

Repeat dose oral toxicity studies conducted with UP446 in rats, mice, and dogs are summarized in Table 3.1.2-1. Generally, UP446 was well tolerated with limited treatment-related effects reported.

In addition to the acute toxicity study described above by Lee *et al*. (2013), the authors also performed a 26-week repeated oral dose toxicity study adhering to OECD GLP (OECD, 1998). In this study, 40-male and 40 female Sprague-Dawley rats were divided into 4 groups of 10 animals each receiving 0, 500, 1,000, or 2,000 mg UP446/kg body weight, mixed in a solution of carboxymethylcellulose sodium salt (0.5%) in water, by oral gavage once daily for 6 months. In addition, 10 male and 10 female rats were used as recovery groups tested 4 weeks after the 26-week treatment, where 5 of each sex were split into the control group or the high-dose group. Mortality, clinical signs, body weight, food consumption, and gross findings were monitored during the experimental period. Ophthalmoscopic examinations, urine analysis, as well as analysis of hematological and biochemical parameters, gross pathology, organ weights, and histopathology were conducted. No death or clinical signs of toxicity were found in any of the groups, except for 1 male and 1 female in the control group. There was no significant difference in body weight found between the groups. Blackish or loose stool were found in certain animals, but this was not considered to be toxic effects due to lack of histopathological change in the gastrointestinal tracks and no change in body weight. There was no test substance related ophthalmological, urinalysis, hematological, histopathological, or absolute and relative internal organ weight effects. In terms of serum clinical chemistry, glucose level was significantly decreased in males at the high-dose compared to controls, but no effects were seen in females. Importantly, there was no significant changes in liver enzymes, absolute and relative liver weight, absolute or relative lung weight, and histopathology.

Burnett *et al.* (2007a) also performed repeat dose toxicity studies on ICR mice and male F344 rats. In the mouse study, 40 male and 40 female mice were split into 4 groups and fed a UP446 formulated diet for 13 weeks that resulted in a dose of 0, 50, 250, or 500 mg UP446/kg body weight/day. In the rat study, 24 young and 24 aged male rats were split into 2 groups and fed a UP446 formulated diet for 9 weeks that resulted in a dose of 0 or 34 mg UP446/kg body weight/day. The evaluated endpoints in these studies were the same as the acute mouse study described above. There were no deaths, effects on body weight, or

histopathological evidence reported during either study. In the mouse study, male mice in the 50 mg UP446/kg body weight/day group developed a decrease in white blood cell count, red blood cell count, hemoglobin level, and mean corpuscular hematocrit when compared to the reference range. Additionally, male and female mice in the 500 mg UP446/kg body weight/day group developed a decrease in platelet count when compared to reference range. While in the rat study, aged rats in the control and 34 mg UP446/kg body weight/day group developed decreased white blood cell counts and increased, aged rats in the control group developed increased mean cell hemoglobin and all rats at both doses developed increased potassium levels compared to reference ranges. Additionally, treated aged rats were reported to have mild to moderate glomerulonephropathy; however, it was not considered treatment-related. Like the acute mouse study described above, statistics on these findings were not reported. Importantly, both repeat dose oral toxicity studies in mice and rats showed no effects on liver enzymes or liver histopathology.

Yimam *et al.* (2010) performed a 90-day oral toxicity study of UP446 in Sprague-Dawley rats. Forty male and 40 female rats were distributed randomly into 4 groups consisting of 0, 250, 500, or 1,000 mg UP446/kg body weight/day *via* oral gavage mixed in a solution of carboxymethylcellulose sodium salt (0.5%) in water. The control group received the vehicle only. The evaluated endpoints included; clinical observations, body weight and feed consumption, ophthalmic evaluation, functional observation battery, motor activity, clinical pathology, sperm count, estrus stage, necropsy, and histopathology. There were no deaths during the duration of the study. There were no test substance related effects on body weight, feed consumption, functional behavior, ophthalmology, motor activity, sperm counts, or estrus cycle. The authors reported no adverse changes in hematology or clinical chemistry parameters; however, there some statistically significant changes including (i) an increase in mean corpuscular volume, mean corpuscular hematocrit, and total bilirubin in female rats fed 1,000 mg UP446/kg body weight/day, (ii) a decrease in absolute monocyte count and increase in blood sodium in female rats fed 500 mg UP446/kg body weight/day, and (iii) a decrease in urine pH in male rats fed 500 or 1,000 mg UP446/kg body weight/day. In terms of gross necropsy, there was a decrease in relative thymus weights in male rats fed 1,000 mg UP446/kg body weight/day and in female rats fed 500 mg UP446/kg body weight/day. Additionally, there was an increase in relative brain weight in female rats fed 500 mg UP446/kg body weight/day. There was no treatment-related macroscopic or microscopic changes. Importantly, there no significant adverse effects of UP446 on liver enzymes, liver and lung weights, as well as liver and lung histopathology. A dose of 1,000 mg/kg/day was identified as the no-observed adverse- effect level (NOAEL) in this study.

Finally, Yimam *et al.* (2016b), reported a study on 16 male and 16 female beagle dogs split into 4 groups treated with 0, 250, 500, or 1,000 mg UP446/kg body weight/day *via* oral gavage for 26 weeks. Two additional animals of each sex were used as recovery groups (2 for the control and 2 for the high-dose group). The study was conducted in compliance with the OECD GLP (OECD, 1998). The evaluated endpoints included ophthalmoscopic examinations, electrocardiograms, urine analysis, clinical chemistry, and histopathology. There was no treatment-related sign of morbidity or mortality, ophthalmological or electrocardiography (ECG) abnormalities, weight gain rate, or urine analysis observed in the duration of the study. There were some hematological parameters with statistical significance; however, due to lack of dose dependence, these changes were considered not toxicologically relevant. Additionally, there were no evident hematology changes in the recovery groups. There were again some clinical chemistry parameters with statistical significance, including an increase in alanine transaminase (ALT) in females receiving 250 mg UP446/kg body weight/day after 26 weeks; however, due to lack of dose dependence, these changes were considered not toxicologically relevant. There was a decrease in absolute brain weight of males receiving 500 mg UP446/kg body weight/day after 26 weeks. Finally, there were no treatment-related changes in histopathology in any of the organs tested including the liver and lung.

From the studies described above, NOAELs for mice, rats, and beagle dogs can be concluded. In mice, no significant treatment-related effects were reported after animals received UP446 *via* oral gavage at up to 500 mg/kg body weight/day, which was considered as the NOAEL in this study (Burnett *et al.*, 2007a). In rats, NOAELs of 34 to 2,000 mg UP446/kg body weight/day were reported in studies in which male and female rats were administered dietary or gavage doses of 34 to 2,000 mg UP446/kg body weight/day for up to 26 weeks (Burnett *et al.,* 2007a; Yimam *et al.*, 2010; Lee *et al.,* 2013). In most cases the reported effects were considered incidental and not related to the treatment of UP446. Finally, in beagle dogs, frequent vomiting and emesis were reported in animals receiving the highest tested dose of 1,000 mg UP446/kg body weight/day for 26 weeks. Due to the prominent emesis and diarrhea were observed in dogs in the high-dose group, the NOAEL was reported to be the second highest dose of 500 mg UP446/kg body weight/day (Yimam *et al.,* 2016b).

Table 3.1.2-1 Summary of Repeat Dose Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Rats, Sprague–Dawley (Hsd:SD) 10/sex/group	Oral (gavage)	90-day oral (gavage) toxicity study	UP446 mixed in 0.5% carboxymethylcellulose solution with water	0, 250, 500, 1,000	• Clinical observations • Body weight and feed consumption • Ophthalmic evaluation • Functional observation battery • Motor activity • Clinical pathology • Sperm count • Estrus stage • Necropsy • Histopathology	• Increased MCV and MCH [F, 1,000] • Decrease in absolute monocyte count [F, 500] • Increase in total bilirubin concentration [F, 1,000] • Decreased relative thymus weights [M, 1,000; F, 500] • Increased relative brain weight [F, 500] • Increase in blood sodium [F, 500] • Decrease in urine pH [M, 500, 1,000]	Yimam *et al.* (2010)
Male dogs (beagle) 4 (single treatment group[c])	Oral (gavage)	Oral (gavage) with ascending dose levels	UP446 mixed in 0.5% carboxymethylcellulose sodium salt solution with water	0, 250, 500, 1,000[d]	• Cardiovascular system effects	• Vomiting reported in 1 control and 1 animal at 500 mg/kg • No statistically significant or biologically relevant change in blood pressure, heart rate, or electrocardiogram parameters	Yimam *et al.* (2016a)
Male rats (Sprague-Dawley) 6 to 8/group	Oral	Oral[e]	UP446 mixed in 0.5% carboxymethylcellulose sodium salt solution with water	0, 800, 2,000, 5,000	• Central nervous system evaluation	• Increase in fecal pellets, 9 hours post-dosing [2,000], and 24 hours post-dosing [2,000, 5,000] • Increase in forelimb grip strength 1 hour after dosing [800]	Yimam *et al.* (2016a)

[a] Unless stated otherwise, all reported effects are statistically significantly different relative to control group(s).
[b] Information in [ ] correspond to the dose in which the reported effects were observed.
[c] Dogs were surgically implanted with telemetry transmitters to monitor the cardiovascular system.
[d] Each animal was provided with 1 dose weekly in ascending order.
[e] Effects on central nervous system in conscious Sprague-Dawley rats; duration not reported.

Table 3.1.2-1 Summary of Repeat Dose Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Male rats (Sprague-Dawley) 6/group	Oral	Single oral dose[f]	UP446 mixed in 0.5% carboxymethylcellulose sodium salt solution with water	0, 800, 2,000, 5,000	• Respiratory evaluation	• No statistically significant or biologically relevant changes in respiratory rate, tidal volume, or minute volume when compared to the control, prior to or up to 24 hours after dosing	Yimam *et al.* (2016a)
Dogs (beagle) 4/sex/group (main group) 2/sex/group (recovery group)	oral (gavage)	26-week repeated oral (gavage) dose toxicity study	UP446 mixed in 0.5% carboxymethylcellulose sodium salt solution with water	0, 250, 500, 1,000 (main group) 0, 2,000 (recovery group)	• Ophthalmoscopic examinations • Electrocardiograms • Urine analysis • Clinical chemistry • Histopathology	• Dose-dependent increase in the duration and severity of emesis and diarrhea • Increase in RBC, HGB and HCT [M, 250, 1,000], and MCV [M, 1,000] after 13 weeks • Decrease in APTT after 26 weeks [F, 250] • Decrease in RBC, HGB, HCT [M, 250, 1,000] and basophils [M, 1,000] after 26 weeks • Increase in MCHC in females after 26 weeks [F, 1,000] • Decrease in globulin alpha 1 [M, 250] alb and A/G ratio [F, 1,000] after 13 weeks • Increase in total cholesterol [M, 1,000] total globulin alpha 1 [F, 250], Crea, T-chol, globulin alpha 2 [F, 1,000] after 13 weeks • Increase in ALT [F, 250] and Glu [F, 1,000] after 26 weeks • Decrease in absolute brain weight [M, 500]	Yimam *et al.* (2016b)

[f] Evaluation of respiratory function in conscious Sprague-Dawley rats; duration not reported.

Table 3.1.2-1 Summary of Repeat Dose Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Sprague-Dawley rats 10/sex/group (main group) 5/sex/group (recovery group)	Oral (gavage)	26-week repeated oral dose toxicity study	UP446 mixed in 0.5% carboxymethylcellulose sodium salt solution with water	0, 500, 1,000, or 2,000 (main group) 0, 2,000 (recovery group)	• Mortality • Clinical signs • Body weight • Food intake • Gross findings • Ophthalmoscopic examinations • Urine analysis • Hematological and biochemical parameters • Gross pathology • Organ weights • Histopathology	• One male and 1 female death in the control group • Blackish stool [500, 1,000, 2,000] • Loose stool in 1 animal [M, 1,000] • Decrease in erythrocyte count, hemoglobin and hematocrit when compared to the control [F, 2,000] • Decrease in blood glucose [M, 2,000] • Increased absolute adrenal weight when compared to the control [F, recovery group]	Lee *et al.* (2013)
Mice (ICR) 10/sex/group	Oral (diet)	13-week subchronic oral study	UP446 in formulated diets	0, 50, 250, 500	• Clinical and behavioral signs • Food and water consumption • Gross necropsy • Histological changes • Hematological parameters • Serum biochemical parameters	• Decrease in WBC, RBC, HGB, and MCH when compared to reference range[g] [M, 50] • Decrease in PLT when compared to reference range[h] [M/F, 500]	Burnett *et al.* (2007a)

[g] Suckow MA, Danneman P, Brayton C (2001). *The Laboratory Mouse*. (Laboratory Animal Pocket Reference Series). Boca Raton (FL): CRC Press Inc.; Gad A, Chengelis CP (1992). *Animal Models in Toxicology*. New York (NY): Marcel Dekker Incorporated.

[h] Mid-Atlantic Regional Laboratory, 10-week-old male and female mice. Mitruka BM, Rawnsley HM (1977). *Clinical and Hematological Reference Values of Normal Experimental Animals*. New York (NY): Masson Publishing.

Table 3.1.2-1 Summary of Repeat Dose Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Male rats[i] (F344) 12/group	Oral (diet)	9-week subchronic oral study	UP446 in formulated diets	0, 34	• Clinical and behavioral signs • Food and water consumption • Gross necropsy • Histological changes • Hematological parameters • Serum biochemical parameters	• Treated aged rats were reported to have mild to moderate glomerulonephropathy; however, it was not considered treatment-related • Decreased WBC in aged rats when compare to reference range[j] [0, 34] • Increased MCH in aged rats when compared to reference range [0] • Increased potassium in all rats when compared to reference ranges [0, 34]	Burnett *et al.* (2007a)

Alb = albumin; A/G = albumin/globulin; ALT = alanine transaminase; APTT = activated partial thromboplastin time; bw = body weight; Crea = creatine; F = female; glu = glucose; HCT = hematocrit; HGB = hemoglobin; M = male; MCH = mean corpuscular hematocrit; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PLT = platelet count; RBC = red blood cell count; T-chol = Total cholesterol; WBC = white blood cell count.

[i] Groups of 12 aged and 12 young rats were used.
[j] Standard values from Harlan Sprague Dawley Inc.

3.1.3 Reproductive and Developmental Toxicity Studies

Reproductive and developmental studies for UP446 in rabbits and rats are summarized in Table 3.1.3-1. Animals were provided doses of 250 to 1,000 mg UP446/kg body weight/day and evaluated for effects on embryo-fetal development, prenatal and postnatal development, maternal function, fertility and early embryonic development. No significant treatment-related effects were reported in any of the evaluated reproductive or developmental endpoints, and the resultant NOAELs were reported to be at or greater than the highest dose tested of 1,000 mg UP446/kg body weight/day (Yimam *et al.*, 2015a-c).

In the study by Yimam *et al.* (2015a), the authors studied the oral effects of UP446 on embryo-fetal development. Ten male and 84 female New Zealand white rabbits were used for artificial insemination, and then the inseminated females were split into groups of 18, 21, 18, and 20, corresponding to doses of 0, 250, 500, and 1,000 mg UP446/kg body weight/day (0.5% carboymethylcelluose-sodium solution used as vehicle and control), respectively, for 13 days from Gestation Day 6 to 18 *via* oral gavage. The study was conducted in compliance with OECD Guideline 414 and GLP (OECD, 1998, 2001). The evaluated endpoints included clinical signs, body weights, food consumption, necropsy, organ weights, caesarean sectioning, external fetus and placenta examination, live fetal body weight, placental weight, visceral examinations, and skeletal examinations. The authors found no significant treatment-related effects on any reproductive or developmental parameter examined; however, there are minor statistically significant changes described in Table 3.1.3-1. Yimam *et al.* (2015a) also performed a study using 96 male and 96 female Sprague Dawley rats for mating, and then the females were split into groups of 21, 22, 22, 21, corresponding to doses of 0, 250, 500, and 1,000 mg UP446/kg body weight/day (0.5% carboymethylcelluose-sodium solution used as vehicle and control), respectively, for 12 days from Gestation Day 6 to 17 *via* oral gavage. The study was also conducted in compliance with OECD Guideline 414 and GLP (OECD, 1998, 2001). This rat study evaluated the same endpoints as the rabbit study by Yimam *et al.* (2015a). Like the rabbit study, the authors found no significant treatment-related effects on any reproductive or developmental parameter examined; however, there are minor statistically significant changes described in Table 3.1.3-1. Notably, there was no treatment-related effect on relative liver weight or visceral findings related to the liver at any dose in the rabbits or rats.

In a follow up study Yimam *et al.* (2015b) studied the oral effects of UP446 the effects on prenatal and postnatal development, including maternal function. The authors used 96 male and 96 female Sprague Dawley rats for mating, and then the females were split into groups of 21, 22, 21, 22, corresponding to doses of 0, 250, 500, and 1,000 mg UP446/kg body weight/day (0.5% carboymethylcelluose-sodium solution used as vehicle and control), respectively, from Gestation Day 6 to Day 20 of lactation *via* oral gavage. The study was carried out under GLP settings. The evaluated endpoints included clinical signs, body weight, food consumption, delivery observations, culling, F1 growth and development, F1 sexual function, necropsy, and organ weights. The authors reported very minimal test-related adverse effects; however, minor statistically significant changes are described in Table 3.1.3-1. Notably, there was no treatment-related effects on relative liver weights at any of the doses for the F0 and F1 generation, and no abnormal macroscopic findings were reported.

Finally, Yimam *et al.* (2015c) studied the oral effects of UP446 on fertility and early embryonic development to implantation. The authors used 88 male and 88 female Sprague Dawley rats split into 4 groups with doses of 0, 250, 500, and 1,000 mg UP446/kg body weight/day (0.5% carboymethylcelluose-sodium solution used as vehicle and control) *via* oral gavage. Males were treated 4 weeks before mating and up to the day before necropsy, while females were treated 2 weeks before mating and through implantation. The study was carried out under GLP settings. The evaluated endpoints included clinical signs, body weights, food

consumption, estrus cycle observations, mating, implantation sites and embryo mortality, necropsy, organ weights, histopathology, and sperm examination. The authors reported no treatment-related effects on reproductive function, sperm motility nor morphology, estrus cycle, necropsy, and histopathology; however, minor statistically significant changes are described in Table 3.1.3-1. Notably, necropsy only found a minor non-dose-related finding of yellowish discoloration at the caudate lobe of the liver in 1 rat treated with 250 mg UP446/kg body weight/day, and a yellow focal spot on the right later lobe of the liver in 1 rat treated with 500 mg UP446/kg body weight/day. There was no significant change in absolute and relative liver weight at any dose in males or females. Additionally, histopathology on the liver and lung with bronchi were evaluated but no adverse effects were reported.

Table 3.1.3-1 Summary of Reproductive and Developmental Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration and Exposure Period	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Rabbits (New Zealand White) (10M, 84F) 18, 20 or 21F/dose	Oral (gavage); once daily for 13 days (Days 6 to 18 of gestation)	Oral effects on effects on embryo-fetal development	UP446 (0.5% carboymethylcelluose-sodium solution used as vehicle and control)	0, 250, 500, 1,000	• Clinical signs • Body weights • Food consumption • Necropsy • Organ weights • Caesarean sectioning • External fetus and placenta examination • Live fetal body weight • Placental weight • Visceral examinations • Skeletal examinations	• One female found dead on Day 22 of gestation due to technical error [250] • Transient decrease in food consumption during the dosing period [F, 250, 500, 1,000] • One animal noted to have cecum discoloration and adhesion to the omentum, enlarged right atrium with a blood clot, and a right atrioventricular nodule [250] • One control female had aplasia of the right uterus horn • Right adrenal gland nodule noted in 2 females [1 each 250, 500] • No significant treatment-related effects on any reproductive or developmental parameter examined	Yimam *et al.* (2015a)
Rats (Sprague Dawley) (96M, 96F) 21 or 22F/dose	Oral (gavage); once daily for 12 days (Days 6 to 17 of gestation)	Oral effects on effects on embryo-fetal development	UP446 (0.5% carboymethylcelluose-sodium solution used as vehicle and control)	0, 250, 500, 1,000	• Clinical signs • Body weights • Food consumption • Necropsy • Organ weights • Caesarean sectioning • External fetus and placenta examination • Live fetal body weight • Placental weight • Visceral examinations • Skeletal examinations	• Spleen enlargement and discoloration, adrenal nodules, and thymus adhesion to the trachea were reported [dose NR] • One fetus reported to have anury [250] • No significant treatment-related effects on any reproductive parameter examined • No significant treatment-related effects on any reproductive or developmental parameter examined	Yimam *et al.* (2015a)
Rats	Oral (gavage);	Oral study on	UP446 (0.5%	0, 250, 500,	• Clinical signs	• One animal found dead on Day 7 of	Yimam *et*

[a] Unless stated otherwise, all reported effects are statistically significantly different relative to control group(s).
[b] Information in [ ] correspond to the dose in which the reported effects were observed.

Table 3.1.3-1 Summary of Reproductive and Developmental Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration and Exposure Period	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
(Sprague–Dawley) (96M, 96F) 21 or 22F/dose	once daily (days 6 of gestation to Day 20 of lactation)	the effects on prenatal and postnatal development, including maternal function	carboymethylcelluose-sodium solution used as vehicle and control)	1,000	• Body weight • Food consumption • Delivery observations • Culling • F1 growth and development • F1 sexual function • Necropsy • Organ weights	gestation due to technical gavage error [1,000] • Reddish-brown stool reported during Days 5 to 19 of dosing [4 animals, 500] and Days 2 to 37 of dosing [21 animals, 1,000] • 16 pups were found deceased during the lactation period [5- control, 3-250, 2- 500, and 6- 1,000] • Post weaning and hematuria observed in 1 male for 4 days [250] • Decrease in body weight reported in males on Postnatal Days 4, 21, and 28 and in females on Postnatal Days 0, 7, 14, 21 and 35 [1,000] • Decrease in body weight reported in females during Postnatal days, Day 35 and 15 of gestation [500] • Decrease in food consumption reported in females on Day 7 and 15 [500] • Increase in the relative brain and heart weight reported [F, 500] • Soft right testes, dark focal spot on liver of 1 male pup [250] • Soft left testes of 2 male pups [500] • Smaller liver size in 1 male pup [1,000]	*al.* (2015b)

Table 3.1.3-1 Summary of Reproductive and Developmental Toxicity Studies

Species (Strain) and Number of Animals	Route of Administration and Exposure Period	Study Design	Chemical	Dose mg/kg bw/day (concentration)	Evaluated Endpoints	Reported Effects[a,b]	Reference
Rats (Sprague–Dawley) (88M, 88F) 22/sex/dose	Oral (gavage) once daily Males: 4 weeks 4 weeks before mating and up to the day before necropsy Females: 2 weeks before mating and through implantation[c]	Oral study on the effects on fertility and early embryonic development to implantation	UP446 (0.5% carboymethylcelluose-sodium solution used as vehicle and control)	0, 250, 500, 1,000	• Clinical signs • Body weights • Food consumption • Estrus cycle observations • Mating • Implantation sites and embryo mortality • Necropsy • Organ weights • Histopathology • Sperm examination	• Reddish brown stool [M and F, 1,000] • Slight decrease in food consumption on Days 0 [M, 1,000] and 21 [M, 500, 1,000] • Increase in implantation indices [F, 250, 1,000] • Decrease in embryo mortalities [1,000] • In 1 rat, seminiferous tubular atrophy (left testis), increased cell debris and decreased sperm number (right epididymal duct) was reported [1,000]	Yimam *et al.* (2015c)

bw = body weight; F = female animals; M = male animals; NR = not reported.

[c] Seven days after confirmation of mating.

3.1.4 Genotoxicity Studies

The genotoxic potential of UP446 was evaluated in a bacterial reverse mutation (Ames) test adhering to OECD Guideline 471 (OECD, 1997; Burnett *et al.*, 2007a). UP446 was diluted in dimethyl sulfoxide to concentrations ranging from 5 to 5,000 µg/plate and plated with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102, with and without metabolic activation. One plate was used per dose level, and 3 plates for both the vehicle and negative control. Genotoxic potential and cytotoxicity was determined by measuring the number of His- to His+ revertant in each strain. No biologically significant increase in mutagenicity was reported at any dose level in any tested strain, with and without metabolic activation. Some moderate to marked signs of cytotoxicity were noted at concentrations of 79 to 5,000 µg/plate in TA100, TA1535 and TA1537. These results support a lack of genotoxic potential for UP446 (Burnett *et al.*, 2007a).

Table 3.1.4-1 Summary of Genotoxicity Studies

Test	Extract Type	Test System/ Animal Species	Concentration	Results	Reference
***In vitro* studies**					
Bacterial reverse mutation (Ames) test	UP446	*Salmonella Typhimurium* strains TA98, TA100, TA1535, T A1537 and TA102	5 to 5,000 µg/plate (diluted in dimethyl sulfoxide); ±S9	Negative (±S9)	Burnett *et al.* (2007a)

+S9 = with metabolic activation; -S9 = without metabolic activation.

3.1.5 Other Studies

The toxicity of UP446 to cells was tested in human cells (Burnett *et al*., 2007a). In this study, a human THP-1 monocyte cell line (ATCC TIB-202) was exposed in triplicate to UP446, along with celecoxib, indomethacin, ibuprofen and aspirin (each in separate assays) at increasing concentrations ranging from 0.2 and 100 µg/mL. Cell damage was monitored by the release of lactate dehydrogenase. Low toxicity for UP446 to the cell line was reported only in the highest tested concentration.

3.1.6 Safety of Individual Components

3.1.6.1 Toxicology Studies

Traditional toxicity studies for *S. baicalensis* and *A. catechu* are limited. Administration of 2, 8, or 32 g/kg body weight/day of an aqueous extract of *S. baicalensis* containing 38.39 mg baicalin/g *via* oral gavage to pregnant mice on Gestation Days 6 to 15 had no significant adverse effects on the number of live or dead fetuses, resorptions, the incidence of post-implantation loss, or on the incidence of fetal external or skeletal malformations (Tian *et al.*, 2009). No maternal death or abortion was found in any group throughout the whole experimental period. There were no obvious signs of toxicity noted in any of the animals. Water and food consumption were normal in all groups, and the number of pregnant mice in all groups was comparable. Maternal absolute liver and kidney weights in the high-dose group were significantly higher than those in negative control group. Relative liver and kidney weights in this group were also significantly higher than those in any other group. However, these changes in organ weight were not corroborated by histology, as no pathological observation in the hematoxylin and eosin (H+E) staining of liver, kidney, and heart sections was detected.

The effects of chronic oral administration of an ethanol extract of *S. baicalensis* (SBE) were evaluated by Yan *et al.* (2018). Eighty male and 80 female Wistar rats were split into 4 groups of 20 animals/sex and received oral gavage doses of SBE for up to 26 weeks, at doses of 0, 300, 1,250, or 2,500 mg/kg body weight/day. Animals were sacrificed at the end of Week 13, Week 26, or after 4 weeks of recovery time. No unscheduled deaths occurred during the experiment. Behavior, gait, general activity, fecal and urine output of rats in all groups showed no obvious abnormalities. There was no significant difference in body weight or food consumption.

The liver tissue showed some inflammatory change that were predominated by leukocyte infiltration but returned to normal after withdrawal. In addition, high-dose SBE treatment of 26 weeks in rats, resulted in changes in plasma glucose, electrolyte and lipid levels. No other functional or organic lesions related to SBE treatment were reported. No significant changes were seen in urinalysis parameters.

After 13 weeks, white blood cells were significantly reduced in males in the 300 and 1,250 mg/kg body weight/day treatment groups compared to controls group, but values remained within the normal range. After 26 weeks of treatment, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentrations were significantly reduced in all treated females. No other effects were seen on hematological parameters. No significant differences were reported after the 4-week recovery period.

A significant and dose-dependent decrease in prothrombin time (PT) in females and a significantly reduced activated partial thromboplastin time (APTT) was reported in males. The PT and APTT values of all groups returned to normal by the end of the recovery period. Sporadic changes were seen in some hematology and serum biochemistry parameters, but these were not considered by the authors to be toxicologically significant. No significant change in the rats' serum enzymes associated with liver injury such as aspartate transaminase (AST), ALT, alkaline phosphatase (ALP), γ-glutamyl-transferase (GGT) were observed.

No changes were seen upon macroscopic examination. The relative liver weight of female rats was significantly higher than that of control rats and tended to remain increased even after the 4-week recovery period. A large number of leukocytes was seen in the liver of high-dose male and female rats at the end of the 26-week treatment period. However, these changes had resolved after a 4-week recovery period. No other pathological changes were seen (Yan *et al*., 2018).

3.1.6.2 Pharmacological Studies

Numerous studies examining the pharmacological effects of the *S. baicalensis* and *A. catechu* are available in the literature. A comprehensive review of these studies is beyond the scope of this report; however, information related to potential effects on the lungs and liver, the 2 organs of potential toxic concern reported by the FDA were evaluated closely.

S. baicalensis was shown to protect against lipopolysaccharide-stimulated (LPS) inflammation *in vitro*. In LPS-stimulated ICR mice, *S. baicalensis* attenuated pulmonary histological changes, lung edema, reduced the inflammatory cell infiltration into lung tissue and inhibited the release of inflammatory cytokines in bronchoalveolar lavage fluid. (Chen *et al.*, 2017). Ethanol extracts of *S. baicalensis* were also reported to be protective against lipopolysaccharide (LPS)-induced liver injury in mice. Pre-treatment with 200 mg/kg body weight/day of *S. baicalensis* extract inhibited LPS-induced increases in tumor necrosis factor alpha, interleukin-1b, interleukin-6, cyclooxygenase-2, inducible nitric oxide synthase, and nuclear factor-kB in liver tissues (Thanh *et al.*, 2015). Dong *et al.* (2016) reported hepatoprotective effects against alcohol-induced liver injury.

An ethyl acetate extract of Acacia catechu provided significant protection against carbon tetrachloride- or iron-induced liver injury in rats (Jayasekhar *et al.,* 1997; Pingale, 2010; Hazra *et al.*, 2013). Similarly, pre-treatment with 200 or 400 mg/kg body weight/day of methanolic bark extract of Acacia catechu for 76 days ameliorated benzo(a)pyrene-induced lung toxicity in mice through the reduction of oxidative stress, inflammation, and apoptosis in mice (Shahid *et al.*, 2017).

3.2 Clinical Studies

3.2.1 UP446

The safety of the oral administration of UP446 was tested in humans in a single-center, randomized, double-blind, placebo-controlled study (Burnett *et al.*, 2007a). In this trial, 80 healthy male and female adults (aged 40 to 75 years) were randomly assigned to receive once daily treatments of 250 mg UP446 or an identical control for 60 days. Dietary guidance was not provided, and no restrictions on exercise were made. The endpoints used to evaluate the safety of UP446 were treatment-related adverse effects and laboratory anomalies. Results were obtained from 29 subjects in the treatment group and 39 subjects in the placebo group. The treatment of UP446 was well tolerated, and adverse effects were typically mild and comparable to the control group. Symptoms reported in the treatment group included drowsiness, irritability, dizziness, insomnia, fatigue, nervousness, disturbing dreams, rash, heartburn, flu-like symptoms, sinus infections, myalgias, and water retention. Mean values for measured plasma biochemistry were all reported to be within clinically acceptable ranges for the treatment group (Burnett *et al.*, 2007a).

The safety and efficacy of UP446 was compared to that of placebo and celecoxib in a randomized, double blind, placebo and active controlled pilot study. Sixty subjects (age 40 to 75) with symptomatic osteoarthritis of the hip or knee were split into groups of 15, to receive placebo carboxymethylcellulose capsule (5 male and 10 female), 250 mg/day UP446 (6 male and 9 female), 500 mg/day UP446 (5 male and 10 female), or 200 mg/day celecoxib (6 male and 9 female). Significant improvements in physical function, endurance and mental health scores were observed for all active treatment groups compared to placebo; however, only UP446 produced significant improvements in the Western Ontario and McMaster University Osteoarthritis Index stiffness and functional impairment scores. No significant changes suggestive of toxicity in routine hematologies, serum chemistries, liver enzymes, or PTT were noted in any of the treatment groups (Sampalis and Brownell, 2012).

3.2.2 Baicalein

Elevated AST and ALT levels were also reported in 4 of 30 subjects consuming baicalein in doses of 200, 400, and 800 mg once daily on Days 1 and 10, twice daily on Days 3 to 9. Additional details were not provided, and the authors considered the treatment to be safe and well tolerated (Pang *et al.*, 2016)

3.3 Adverse Events

Unigen's proprietary botanical ingredient Univestin® has been sold successfully for over 15 years. Based on sales figures provided by Unigen more than 5.7 billion servings/doses (125 mg) have been sold in over 14 countries spanning the globe during this time period.

No case reports have been identified in the literature indicating any adverse effects of Univestin®. Although cases of drug induced liver injury (DILI) and hypersensitivity pneumonitis an immune mediated lung disease associated with Move Free® were identified in the literature, it is not clear how the composition of this product compares to that of Univestin®, although at least some formulations of this supplement do contain extracts of *S. baicalensis* and *A. catechu*. Although there were no case reports related to Univestin® in the literature, 6 adverse events or product complaint reports associated with Univestin® were found in the FDA's Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS). Several other reports in CAERS involved Move Free® supplements. Additional details follow.

3.3.1 Drug-Induced Liver Injury

DILI can be triggered by a drug and/or its metabolites, or as a reaction of hypersensitivity to the compound. A wide variety of drugs can cause DILI, including chemotherapy drugs, anti-tuberculosis drugs, antipyretic analgesics, immunosuppressive agents, and antibacterial, antifungal and antiviral drugs. Drugs and their reactive metabolites covalently bind to mitochondria and cause direct hepatic toxicity through accumulation of oxidative stress (reactive oxygen species [ROS] and reactive nitrogen species [RNS]), endoplasmic reticulum stress and mitochondrial dysfunction, ultimately leading to cell death (Ye *et al*., 2018). Patients with DILI often present features such as including elevated liver enzymes, hepatitis, hepatocellular necrosis, cholestasis, fatty liver and liver cirrhosis. Serum aminotransferases, that is, ALT and AST, ALP and total bilirubin (TB) levels, although not specific for DILI, remain the standard for detecting and classifying liver damage (Kullak-Ublick *et al.,* 2017).

Four cases of hepatoxicity were attributed to Move Free®, a dietary supplement containing a proprietary anti-oxidant blend of herbs including S. *baicalensis* and *A. catechu* among the 14,999 cases in the Drug-Induced Liver Injury Network (DILIN) between 2004 and March 2015. All 4 cases involved adult females (37 to 88 years of age) who developed acute hepatitis with autoantibodies after a relatively short exposure. Liver biopsies completed in 3 subjects revealed inflammatory infiltrates of lymphocytic and plasma cells. The authors reported these findings were consistent with immune mediated injury, possibly in predisposed autoimmune hepatitis (AIH) individuals (Do *et al*., 2015). It is not clear how the composition of Move Free® compares to that of Univestin®.

Additional details of some of these cases were available in case reports of DILI associated with Univestin® or related supplements (*e.g.*, Move Free®, *S. baicalensis*, or baicalein) were available in the literature.

Linnebur *et al*. (2010) reported 2 potential cases of DILI associated with Move Free® Advanced, a supplement containing glucosamine, chondroitin, hyaluronic acid, *S. baicalensis*, and *A. catechu*), along with methylsulfonylmethane (MSM). A 71-year-old Caucasian woman presented with complaints of diarrhea, increased fatigue, and mild depression that developed slowly over the previous 2 weeks. The patient had initiated supplementation with Move Free® Advanced 1 week prior to the onset of symptoms. Her medical history was significant for hypertension, allergic rhinitis, and osteoarthritis. Her drug therapy consisted of atenolol, mometasone nasal spray, a multivitamin, flax seed oil, calcium with vitamin D, and Move Free® Advanced, dosed according to the product recommendation (2 tablets/day).

Hepatic function test results (bilirubin, AST, ALT, ALP, and GGT) were extremely elevated, up to 9 times the upper limit of normal. Abdominal ultrasonography revealed no hepatic abnormalities other than mild fatty infiltration. The patient also reported mild-to-moderate abdominal cramping associated with diarrhea, chromaturia, and fatigue. Serology studies were negative for hepatitis A, B and C. Three to 4 weeks after stopping the supplement, the patient's hepatic function test results improved, with normalization occurring

approximately 12 weeks after discontinuation. The patient did not suffer any serious or life-threatening consequences due to the hepatic injury.

A second case reported by these authors involved an 85-year-old Caucasian woman. Although the patient reported no specific symptoms, routine bloodwork revealed slightly elevated bilirubin and liver enzymes after 3 weeks after initiation of supplementation with Move Free® Advanced. Her medical history consisted of chronic cough, hypothyroidism, allergic rhinitis, recurrent urinary tract infections, osteoarthritis, peptic ulcer disease and hysterectomy. Her drug therapy consisted of levothyroxine, loratadine, guaifenesin with dextromethorphan as needed for cough, Centrum Silver (Wyeth Consumer Healthcare, Madison, NJ), vitamin E, lutein, magnesium oxide, Move Free® Advanced plus MSM, and as-needed use of a dietary supplement, WishGarden Herbs Serious Cough Medicine (WishGarden Herbs, Inc., Boulder, CO; contains wild cherry bark, grindelia flower, goldenseal root, pleurisy root, licorice root, lobella herb, coltsfoot leaf, mullein leaf, echinachea root and leaf in ~55% organic alcohol and Rocky Mountain water). On her doctor's recommendation, the woman stopped use of the supplement, and within 7 weeks, her hepatic function panel essentially normalized (Linnebur *et al.,* 2010). The authors also reviewed online resources and databases and identified other cases of hepatoxicity in patients consuming combination products containing *S. baicalensis.*

Yang *et al.* (2012) reported the case of a 78-year old Caucasian woman initially presented with acute painless jaundice 3 weeks after initiating supplementation with Move Free® Advanced. The patient's medical history was significant for osteoarthritis and hyperlipidemia. Past surgical history included a cholecystectomy. She was not on any prescription medications but took a multivitamin daily and had started Move Free® Advanced®, a glucosamine/chondroitin supplement with a recommended dose of 1 tablet twice a day.

Serum bilirubin, AST, ALT, ALP, and GGT were all significantly elevated. Serology studies were negative for hepatitis A, B, and C. Supplementation was discontinued and after 2 weeks later her bilirubin and liver enzyme values had decreased. However, within 2 weeks after resuming supplementation, the patient experienced jaundice and her laboratory studies again revealed increased bilirubin, AST, ALT, and ALP values. Although no changes were seen on computed tomography (CT) scan, liver biopsy showed portal tracts containing mild, predominately mononuclear cell infiltrates, with many eosinophils. There were also significant lobular inflammatory cell infiltrates, including eosinophils. Numerous acidophil bodies were seen and scattered ballooned hepatocytes were also present. No fibrosis was seen, and iron staining was negative. These findings were considered to be consistent with acute drug induced hepatitis. Four weeks after discontinuing the supplement, Move Free® with bilirubin and serum enzyme values had normalized.

Dhanasekaran *et al.* (2013) reported a case of DILI with simultaneous pulmonary infiltrates 2 weeks after commencing use of Move Free®. A 62-year-old Caucasian female presented with acute onset of shortness of breath. She was found to be hypoxic and jaundice, and chest X-ray showed bilateral interstitial infiltrates. In addition, liver function tests revealed elevated aminotransferases and hyperbilirubinemia. No evidence of chronic liver disease was present, and serology, including those for viral and autoimmune hepatitis, were negative. Fatty infiltration of the liver was seen upon abdominal ultrasound, but no evidence of portal hypertension or biliary duct obstruction was seen. A liver biopsy revealed histologic features of a panacinar hepatitis with expansion of the portal tracts by a mixed chronic inflammatory infiltrate composed of lymphocytes, eosinophils, and plasma cells. The lobular parenchyma showed foci of inflammation with scattered eosinophils and acidophil bodies.

Mild steatosis (15 to 20%) with features of a mild superimposed steatohepatitis present without established fibrosis was also observed. In addition, the patient also presented with significant respiratory distress and required oxygen support. CT scan of the chest revealed bilateral ground glass opacities in the upper lobes. Viral and bacterial testing failed to identify an infections etiology to her pulmonary infiltrates. Both the hepatic and pulmonary complications completely resolved over few weeks after the patient stopped taking the medication, with liver enzymes normalizing after 8 weeks.

Burke *et al.* (2014) presented a case report of a 30-year-old man who arrived at the hospital experiencing acute onset jaundice following consumption of Baikal Skullcap (*S. baicalensis*) along with a recent history of alcohol intake. The authors reported extreme elevations in both aspartate aminotransferase and alanine aminotransferase, as well as in bilirubin and the AST/ALT ratio. The liver biopsy was reported to be consistent with drug toxicity. The patient was treated with N-acetylcysteine and liver enzyme levels normalized. In addition, the authors reviewed several other case reports of hepatoxicity associated with *S. baicalensis.* Generally, jaundice onset occurred 2 weeks to 6 months after consuming skullcap, typically in herbal formulations for relaxation. Labs are notable for elevated liver enzymes and total bilirubin. Symptoms and laboratory abnormalities resolve within 2 weeks to 19 months after discontinuing skullcap.

3.3.2 Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an immune mediated lung disease which represents a complex syndrome. It may occur in acute, subacute, or chronic forms. Hypersensitivity pneumonitis is exacerbated by an extrinsic allergen, most often organic aerosols, low molecular weight chemical antigens, and some mediations and results in granulomatous, interstitial, bronchiolar and alveolar filling lung diseases, leading to a presentation similar to interstitial pulmonary fibrosis. Patients experience fever, chills, malaise, cough, chest tightness, dyspnea, and headache (Donato, 2017).

As with DILI, reports in the literature provided additional details of 1 case associated with Move Free®. As previously discussed, Dhanasekaran *et al.* (2013) reported a case DILI with simultaneous pulmonary infiltrates 2 weeks after commencing use of Move Free®, with bilateral interstitial infiltrates visible on chest X-ray. Complications completely resolved over a few weeks after the patient stopped taking the medication.

In addition, the FDA's CFSAN CAERS is a database that contains information on adverse event and product complaint reports submitted to FDA for foods, dietary supplements, and cosmetics. The FDA does not evaluate whether the products listed in CAERS actually caused the adverse events, and information about consumers underlying conditions or concomitant use of other products is limited. Furthermore, these cases may have been duplicates of other case reports in the CAERS database or in the literature. A search for "Univestin" in the CAERS, with data available from January 2004 to September 2017, yields 6 entries. Of these, 1 mentions pneumonitis, 1 mentions abnormal liver function test, and 1 mentions hypersensitivity. No additional details were provided. Similarly, a search for Move Free® produced 72 additional adverse event reports. Of these, 1 mentioned hypersensitivity, 1 mentioned abnormal chest X-ray and 10 mentioned dyspnea, though it is not certain whether any of these cases was classified as hypersensitivity pneumonitis. Sixteen others included symptoms potentially associated with DILI (*e.g.,* elevated liver enzymes and bilirubin, hepatitis, jaundice). It is not clear from the information presented in the database whether these formulations contained *S. baicalensis* and *A. catechu*.

4.0 SUMMARY AND EVALUATION

Univestin® is a proprietary blend of 2 flavonoids: baicalin, derived from the roots of *S. baicalensis*, and catechin, obtained from the bark and heartwood of *A. catechu.* Specifically, Univestin® (UP446) is comprised of *S. baicalensis* extract (≥75%), *A. catechu* extract (≥65%), and USP maltodextrin in the ratio of approximately 80:17:3. Unigen's proprietary botanical ingredient Univestin® has been sold successfully for over 15 years. Based on sales figures provided by Unigen, it has been sold in over 14 countries spanning the globe and has been consumed in more than 5.7 billion doses (125 mg) during this time period.

A series of pre-clinical safety studies have been conducted on Univestin® in mice, rats, and dogs to assess general toxicity following acute, subchronic, and chronic exposure. In addition, the potential effects of Univestin® on developmental and reproductive toxicity has been evaluated in in rats and rabbits. These studies followed international guidelines and are considered of a sufficient quality and quantity to evaluate the safety of Univestin®.

The acute lethal dose of UP446 in rats is greater than 5,000 mg/kg body weight. No deaths or effects on body weight were reported following administration of 2,000 mg/kg body weight/day of UP446 by gavage for 14 days. Red blood cell count was reported to fall below the reference range in male treated mice. Similarly, mean cell volume and platelet count was below the reference range in female treated mice. Liver alanine aminotransferase levels were reported to be above the reference range in treated males only. Statistical analyses of these results were not reported.

No effects on the cardiovascular system of beagle dogs treated with a single dose of UP446 up to 1,000 mg/kg body weight, were reported. Similarly, no adverse effects were seen on central nervous system or respiratory endpoints following administration of single doses up to 5,000 mg/kg body weight. In repeat dose studies, NOAELs of 34 to 2,000 mg/kg body weight/day were reported in studies in which male and female rats were administered dietary or gavage doses or up to 26 weeks. In beagle dogs, frequent vomiting and emesis were reported in animals receiving the highest tested dose of 1,000 mg/kg body weight/day for 26 weeks. In mice, no significant treatment-related effects were reported after animals were fed UP446 *via* oral gavage at up to 500 mg/kg body weight/day. Importantly, there was no significant adverse effects of UP446 on liver enzymes, liver and lung weights, as well as liver and lung histopathology in these studies. No significant treatment-related effects were reported in any of the evaluated reproductive or developmental endpoints, and the resultant NOAELs were reported to be at or greater than 1,000 mg/kg body weight/day. A lack of genotoxic potential for Univestin® was indicated by the results of a bacterial reverse mutation test.

Data on the toxicity of S*. baicalensis* and *A. catechu*, and their active components, baicalin and catechin, respectively, are limited. A recent study of the chronic toxicity of *S. baicalensis* in rats included reports of inflammatory changes in the liver. A large number of leukocytes was seen in the liver of high-dose (2,500 mg/kg body weight/day) male and female rats at the end of the 26-week treatment period. However, these changes had resolved after a 4-week recovery period.

In addition, clinical studies have evaluated the safety and efficacy of UP446 in subjects with OA. In these studies, UP446 was considered safe and well-tolerated. Mean values for measured plasma biochemistry were all reported to be within clinically acceptable ranges following administration of 250 mg UP446 or an identical control to 80 healthy adults for 60 days. Likewise, no significant changes suggestive of toxicity in routine hematologies, serum chemistries, liver enzymes or PTT were noted in subjects receiving 250 mg/day UP446, 500 mg/day UP446, or 200 mg/day celecoxib for 90 days.

There were no reports of adverse effects on the lungs potentially indicative of hypersensitivity pneumonitis in clinical trials with Univestin®. However, hypersensitivity pneumonitis and DILI associated with the use of related supplements have been reported in the literature. Cases reports of DILI associated with Move Free® were identified in the literature. These cases involved elevations of liver enzymes and bilirubin. One case involved simultaneous pulmonary infiltrates. In all reported cases, hepatic function tests normalized following discontinuation of treatment.

While no case reports have been identified in the literature indicating any adverse effects of Univestin®, some reports of hypersensitivity pneumonitis and DILI associated with Univestin® in Move Free®, have been identified in the FDA's CAERS database. A search for "Univestin" in the CAERS, with data available from January 2004 to September 2017 yielded 6 entries. Of these, 1 mentions pneumonitis, 1 mentions abnormal liver function test, and 1 mentions hypersensitivity. No additional details were provided. Similarly, a search for Move Free® produced 72 additional adverse event reports. Of these, 1 mentioned hypersensitivity, 1 mentioned abnormal chest X-ray and 10 mentioned dyspnea, though it is not certain whether any of these cases was classified as hypersensitivity pneumonitis. Sixteen others included symptoms potentially associated with DILI (*e.g.,* elevated liver enzymes and bilirubin, hepatitis, jaundice). It is not clear from the information presented in the database whether these formulations contained *S. baicalensis* and *A. catechu* or how these formulations compare to Univestin®. These adverse reports occur with low frequency and result in mild to moderate, reversible effects on the liver or lungs.

It should be noted that a filing of a CAERS report is not sufficient to prove cause and effect. Thus, the CAERS reports do not prove that Univestin® caused any adverse health effects reported. As stated by the FDA, "*The existence of an adverse event report does not necessarily mean that the product identified in the report actually caused the adverse event*". The FDA carefully investigates and evaluates other possible causes before deciding whether the product actually caused the reported adverse event.

Deficiencies of CAERS that can preclude identification of a cause and effect relationship, as noted by the FDA itself (https://www.fda.gov/food/complianceenforcement/ucm494015.htm) (U.S. FDA, 2017), include:

- "*Reports with incorrect, incomplete or no contact information, which make following up with the complainant difficult or impossible;*
- *Variability among the completeness of the reports. Some reports may consist only of a single sentence with little detail;*
- *Reports that list the brand, but do not identify the specific product;*
- *Absence of or lack of FDA access to other information related to the report, such as medical records and medical histories (In fact, some state medical privacy laws prevent FDA from obtaining medical records related to the adverse event report.);*
- *Use of other supplements or medications at the same time;*
- *Pre-existing or undiagnosed medical conditions;*
- *Improper use of the product*".

No case reports have been identified in the literature indicating any adverse effects of Univestin® and the lack of any identified cause and effect from the CAERS is also corroborated through repeat dose toxicity studies with Univestin®, which revealed no significant adverse effects of UP446 on liver enzymes, liver and lung weights, or liver and lung histopathology. Importantly, no significant changes suggestive of toxicity were seen in clinical studies with Univestin®, and the totality of the information indicates a margin of safety in excess of 100 between the recommended intake of Univestin® (*i.e.*, 250 mg/day, equivalent to 4.2 mg/kg body weight for a 60-kg individual) and the NOAEL of 500 mg/kg body weight/day from the 26-week dog study. The very low number of reports in the FDA CAERS in relation to more than 5.7 billion doses (125 mg) that have been marketed over a 15-year period therefore calls into question the potential association with the administration of Univestin®.

Furthermore, the case reports in the literature that are non-Univestin®-related suggest these effects are in older people, often with underlying medical conditions and consuming multiple drugs or supplements. As a result, again it is not possible to make any firm conclusions with regards to cause.

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