ACCEPTABLE DAILY EXPOSURE AND OCCUPATIONAL EXPOSURE LIMIT MONOGRAPH FOR [redacted]

ADE = [redacted] micrograms/day
OEL = [redacted] micrograms/m^3 (8-hr TWA)
Wipe Limit Criterion: [redacted] micrograms/100cm^2

Synonyms[1]: CAS [redacted]; [redacted], [redacted], [redacted]

Chemical Identity and Physico-chemical properties
[redacted]

Figure 1[1]: Structure of [redacted]

Mechanism of Action and Intended Use
[redacted] is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the estrogen receptor protein in human breast cancer cells[2]. Many breast cancers have estrogen receptors (ER) and the growth of these tumors can be stimulated by estrogen[2]. [redacted] is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy[2].

Animal Data
Acute Toxicity – Oral LD_{50} values of 300, 3200 and 980 mg/kg were reported for the mouse, rabbit, and rat models, respectively[4].

Local Toxicity – [redacted] is moderately irritating to the eyes in the rabbit model[4].

Repeat-Dose Toxicity – [redacted] showed no agonist-type effects in *in vivo* uterotrophic assays in immature or ovariectomized mice and rats. In *in vivo* studies in immature rats and ovariectomized monkeys, [redacted] blocked the uterotrophic action of estradiol[5]. Repeat dose toxicity studies of 6 and 12month duration were conducted in rats and dogs, respectively[3]. The relative doses used on these studies were 4fold higher than the proposed clinical dose of 185 mg/m^2/month[3]. In both rats and dogs, atrophy of the

uterus, cervix, and vagina were observed after long term dosing. Ovarian changes included increase in the size and number of Graffian follicles and a reduction in the number of corpora lutea[3]. In dogs, absence of clinical signs of estrous activity were recorded which was reversible[3]. In male rats after 6 months of dosing, a loss of spermatozoa, seminiferous tubular atrophy, and degenerative changes in the epididymides were seen which did not show evidence of recovery by 4 weeks[3].

Developmental and Reproductive Toxicity – In studies in female rats at intramuscular doses ≥ 0.01 mg/kg/day (0.6% of the human recommended dose based on body surface area [BSA]), ■■■■■■ caused a reversible reduction in female fertility, as well as effects on embryo-fetal development consistent with its anti-estrogenic activity[2]. ■■■■■■ caused an increased incidence of fetal abnormalities in rats (tarsal flexure of the hind paw at 2 mg/kg/day; equivalent to the human dose based on ■■■■■■) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥ 0.1 mg/kg/day when administered during the period of organogenesis[2].

Rabbits failed to maintain pregnancy when dosed intramuscularly with 1 mg/kg/day ■■■■■■ (equivalent to the human dose based on BSA) during the period of organogenesis[2]. In rabbits dosed at 0.25 mg/kg/day, increases in placental weight and post-implantation loss were observed[2]. ■■■■■■ was associated with an increased incidence of fetal variations in rabbits at 0.25 mg/kg/day when administered during the period of organogenesis[2]. Because pregnancy could not be maintained in the rabbit following doses of ■■■■■■ of 1 mg/kg/day and above, this study was inadequate to fully define the possible adverse effects on fetal development at clinically relevant exposures[2].

In female rats, ■■■■■■ administered at doses ≥ 0.01 mg/kg/day (0.6% the human recommended dose based on body surface area [BSA]), for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival[2]. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (0.06% the human dose based on BSA). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (equivalent to the human dose based on BSA). The effects of ■■■■■■ on the fertility of female rats appear to be consistent with its anti-estrogenic activity[2]. The potential effects of ■■■■■■ on the fertility of male animals were not studied but, in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days ■■■■■■ showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides[2]. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing[2]. ■■■■■■ doses correspond to 1.3-, 1.2- and 3.5-fold the systemic exposure achieved in women receiving the recommended dose of 500 mg/month[2].

It is not known if ■■■■■■ is excreted in human milk; however, based on studies in rats it is likely excreted. ■■■■■■ is found in rat milk at levels significantly higher (approximately 12-fold) than plasma after administration of 2 mg/kg[2]. Drug exposure in

rodent pups from ■■■■■■-treated lactating dams was estimated as 10% of the administered dose[2].

Genotoxicity **–** ■■■■■■ was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of Salmonella typhimurium and Escherichia coli, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells, and *in vivo* micronucleus test in rat)[2].

Carcinogenicity **–** A two-year carcinogenesis study was conducted in female and male rats given intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days[2]. These doses correspond to 0.9-, 1.5-, and 3-fold (in females) and 0.8-, 0.8-, and 2-fold (in males) the systemic exposure achieved in women receiving the recommended dose of 500 mg/month[2]. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively[2].

A two years carcinogenicity study was conducted in female and male mice at orally administered doses of 0, 20, 150 and 500 mg/kg/day[2]. These doses correspond to 0, 0.8, 8.4 and 18-fold (in females) and 0, 0.8, 7.1 and 11.9-fold (in males), the systemic exposure achieved in women receiving the recommended dose of 500 mg/month[2]. There was an increased incidence of sex cord stromal tumors (both benign and malignant) in the ovary at doses of 150 and 500 mg/kg/day[2]. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen[2].

Human Clinical Data

Dosages used in Clinical Trials –The recommended dose is 500 mg to be administered intramuscularly slowly (1 - 2 minutes per injection) as two 5 mL injections, on days 1, 15, 29 and once monthly thereafter[2]. Median treatment duration in clinical trials was 6 months[3]. A dose of 250 mg is recommended for patients with moderate hepatic impairment[2]. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to ■■■■■■ treatment of 250 mg monthly suggested no peripheral steroidal effects[2]. In clinical specimens from women with primary breast cancer, the administration of single intramuscular injections of ■■■■■■ at a of dose 50, 125 or 250 mg produced dose-dependent reductions in estrogen receptor expression as compared to placebo[3].

A clinical study of ■■■■■■ was conducted in 30 girls with McCune-Albright Syndrome (MAS) associated with progressive precocious puberty (PPP)[2]. The median age at informed consent was 6 years old with a range of 1 to 8 years[2]. The first 10 patients initially received ■■■■■■ 2 mg/kg[2]. Based on pharmacokinetic data from the first 6 patients, all 10 patients receiving 2 mg/kg were escalated to a dose of 4 mg/kg and all other patients received 4 mg/kg from study entry[2]. Twenty-nine of 30 patients completed the 12-month study period. Thirty five percent of the 23 patients with baseline vaginal bleeding experienced a complete cessation of vaginal bleeding on-treatment (month 0

to 12), a reduction in the rate of bone age advancement during the 12-month study period compared to baseline, and a reduction in mean growth velocity[2]. There were no clinically meaningful changes in mean uterine volume, mean ovarian volume, or predicted adult height (PAH) on-treatment compared to baseline[2]. Eight patients (27%) experienced adverse reactions that were considered possibly related to ■■■■■■. These included injection site reactions, abdominal pain, contusion, tachycardia, hot flush, extremity pain, and vomiting[2].

Adverse Reactions – The most common adverse effects reported with therapeutic use of ■■■■■■ include: nausea, muscle, joint and bone pain, headache, tiredness, hot flashes, vomiting, loss of appetite, weakness, cough, constipation, shortness of breath, and increased liver enzymes[2].

Susceptible Subpopulations – Patients with moderate to severe hepatic impairment are administered half the dose as patients without hepatic impairment[2]. No differences were seen in the pharmacokinetic parameters between males and females, different ethnicities, age or in patients with mild renal or hepatic impairment[3].

Pharmacokinetics and Pharmacodynamics

■■■■■■ is highly lipophilic and does not ionize at physiological pH[3]. Oral delivery was not possible as adequate bioavailability is not achievable[3]. ■■■■■■ is administered by intramuscular injection. The apparent volume of distribution at steady state is approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. ■■■■■■ is highly (99%) bound to plasma proteins; VLDL, LDL and HDL lipoprotein fractions appear to be the major binding components[2]. Biotransformation and disposition of ■■■■■■ in humans have been determined following intramuscular and intravenous administration of ^{14}C-labeled ■■■■■■. Metabolism of ■■■■■■ appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulfate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulfoxide[2]. Identified metabolites are either less active or exhibit similar activity to ■■■■■■ in anti-estrogen models[2]. ■■■■■■ was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance was 690 ± 226 mL/min with an apparent half-life about 40 days[2].

No differences were seen in the pharmacokinetic parameters between males and females, different ethnicities, age or in patients with mild renal or hepatic impairment[3].

The single dose and multiple dose pharmacokinetic parameters for the 500 mg dosing regimen with an additional dose (AD) at Day 15 are reported in Table 1. These data were used to derive a chemical specific adjustment factor[6] of 1.60 for the pharmacokinetic component of the uncertainty factor for interindividual variability.

Table 1: Pharmacokinetic data (Mean±SD) for the derivation of the CSAF for [redacted]

Dose Regimen	AUC	Mean+ 2SD/Mean	Cmax	Mean + 2SD/Mean
Single 50 mg I.M. injection to postmenopausal women with breast cancer	11400±3808	1.67	25.1±8.86	1.71
Three monthly 50 mg I.M. injections to postmenopausal women with breast cancer	13100±3065	1.47	28.0±7.81	1.56
				6.41/4=1.6(3.2)=5.1

Derivation of ADE:
Selection of point of departure (POD);
[redacted]

Intraspecies variability (UF_A);
[redacted]

Interindividual variability (UF_H);
[redacted]

Subchronic to chronic extrapolation (UF_C);
[redacted]

LOEL to NOEL extrapolation (UF_L);
[redacted]

Database completeness (UF_D);
[redacted]

Modifying factor (MF) – A modifying factor;
[redacted]

Bioavailability factor (α);
[redacted]

Steady state factor (S);
[redacted]

ADE = $\frac{\text{LOAEL (mg/day)}}{(UF_A)(UF_H)(UF_L)(MF)(\alpha)}$ = [redacted]

= [redacted] µg/day

Where: ADE = acceptable daily exposure for all exposure routes
LOAEL = low observable adverse dose

Derivation of OEL:
Selection of point of departure (POD);
[redacted]

Intraspecies variability (UF_A);
[redacted]

Interindividual variability (UF_H);
[redacted]

Sub-chronic to chronic extrapolation (UF_C);
[redacted]

LOEL to NOEL extrapolation (UF_L);
[redacted]

Database completeness (UF_D) – UF_D;
[redacted]

Modifying factor (MF) – A modifying factor;
[redacted]

Bioavailability factor (α);
[redacted]

Steady state factor (S);
[redacted]

Derivation of OEL:
To derive an 8hour TWA, the assumption was made that 10 m^3 is the volume of air a 50kg individual breathes in an 8hour workday[8]. Derivation of short term exposure limit (STEL) is not warranted.

$$\textbf{OEL-TWA} = \frac{\textbf{LOAEL (mg/day)}}{(UF_A)(UF_H)(UF_L)(MF)(\alpha)(m^3)} = \frac{\text{[redacted]}}{\text{[redacted]}}$$

$$= \text{[redacted]}\ \mu g/m^3$$

Where: OEL-TWA = occupational exposure limit established as an 8-hour time weighted average
LOAEL = low observable adverse effect dose

In summary, an acceptable daily exposure (ADE) of [redacted] µg/day and an occupational exposure limit (OEL) of [redacted] µg/m^3 are recommended for [redacted] based on a low human clinical dose.

The acceptable daily exposure or ADE is defined as the daily dose of a substance, expressed in mg/day or µg/day, below which no adverse effects are expected in susceptible individuals following exposure for a lifetime by any route, including parenteral administration[9]. The ADE is consistent with the derivation of a permitted daily exposure (PDE) according to the EMA and ICHQ3C guidelines[10, 11].

Excursions in worker exposure levels may exceed 3 times the OEL-TWA for no more than a total of 30 minutes during a workday, and under no circumstances should they exceed 5 times the OEL-TWA, provided that the OEL-TWA is not exceeded. One existing OEL was found for [redacted]. The OEL value found was 1 µg/m^3 established as an 8-hour time weighted average. The lowest therapeutic dose used for the existing OEL value was 8.3 mg/day administered by intramuscular injection.

The occupational exposure limit or OEL is defined as an airborne concentration that is not expected to cause adverse health effects or clinically significant effects in workers handling a material for a working lifetime without benefit of personal protective equipment[8].

An acceptable residual level can be calculated using the ADE and the equation shown in Appendix 1.

References:

[redacted]

Review and Approvals

Prepared: Edward V. Sargent, MPH PhD DABT Signature: Edward Sargent
Managing Director
EV Sargent LLC

Summary of Risk Assessment Report

Company Name: [redacted]

Company Address: [redacted]

Expert Name: Edward V Sargent MPH, PhD, DABT

Date (MM/DD/YR): [redacted]

Chemical Name(s) and CAS Number(s): [redacted]

Specific Hazards Identified

Hazard	YES	NO	UNKNOWN
Positive genotoxicant		x	
Reproductive developmental toxicant	x		
Potential carcinogen		x	
Sensitizing potential			x

Basis for the ADE

Critical effect observed: low observable adverse effect dose

Dose upon which the ADE is based (CV): [redacted] µg/day

Species from which ADE is calculated: Rats

References

[redacted]

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Brief CV

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EV Sargent LLC is a limited liability company organized in February 2007 and existing under the laws of the State of Florida, providing strategic consultation and service in occupational and environmental toxicology, risk assessment and regulatory compliance.

Dr Sargent is the author or co-author of over 150 papers, book chapters and presentations on occupational and environmental toxicology and risk assessment. He has conducted risk assessments of over 600 pharmaceutical compounds resulting in the establishment of occupational exposure limits and/or acceptable daily exposures. Dr. Sargent has been Past President of the Mid Atlantic Chapter of the Society of Toxicology, Member of the Board of Directors of the American Board of Toxicology and of the Risk Assessment Specialty Section of the Society of Toxicology and is currently a Member of the American Conference of Governmental Hygienists Threshold Limit Value Committee.

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Appendix 1: Calculation of an Acceptable Residual Level (ARL)

$$ARL = \frac{(ADE)\,(SBS)\,(SA)\,(RF)\,(CF)}{(MDD)\,(SSA)}$$

Where: ARL is the acceptable residual level (mg/swab)
ADE is the acceptable daily exposure (µg/day)
SBS is the smallest batch size (kg)
SA the swab surface area (cm^2/swab)

RF is the recovery factor (unitless)
CF the conversion factor = 1000 (unitless)
MDD is the maximum daily dose of the drug (mg/day) which is set at 10 g/day based on ICH Q3C(R4) which assumes 10,000 mg/day as an MDD in setting limits for Class 2 solvents
SSA is the shared surface area (cm^2)

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