PDE Determination Strategy for Mometasone Furoate (Topical)

Date of Assessment:

March 2026

Prepared by Prof. Salama A. Salama, BSc. MSc. PhD

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1. BASIC INFORMATION

Company Name	The state company for drugs industry and medical appliances **(SDI)**
Company Address	SAMARRA / IRAQ
Chemical Name	Mometasone Furoate
Date of Assessment	March 2026
Report's expiration date	March 2031
Expert Name	Dr. Salama Abdou Mohamed Salama
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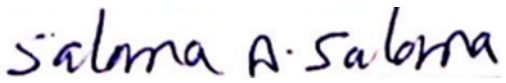
Signature/Date	
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Signature/Date	

Version	Title	Revision Description
1.0	PDE Determination Strategy for Mometasone Furoate (Topical)	**First Issue**

2. HAZARDS IDENTIFIED

	Yes	No	Unknown
Genotoxicity and mutagenicity		X*	
Reproductive and developmental toxicity	X**		
Carcinogenicity		X***	
Highly sensitizing potential		X*[a]	

X*Genotoxicity and mutagenicity of Mometasone Furoate

Mometasone furoate was negative in the Ames bacterial mutagenicity assay, mouse-lymphoma assay, rat bone marrow clastogenicity assay, Chinese hamster lung chromosome aberration assay, and male germ cell clastogenicity assay. At cytotoxic doses, mometasone furoate produced an increase in chromosome aberrations in vitro but not in the presence of microsomal activation (rat liver S9 fraction). [2]

X** Reproductive and developmental toxicity of Mometasone Furoate

In reproductive studies in rats, impairment of fertility was not produced in male or female rats by subcutaneous doses up to 15mcg/kg (approximately 0.01 times the estimated maximum clinical topical dose from mometasone furoate cream, on a mcg/m2 basis). Corticosteroids are known teratogens in rodent species with some teratogenic effects having been observed in non-human primates. They are generally teratogenic in laboratory animals when administered systemically at low dosages. Developmental toxicity studies were conducted with mometasone furoate in rats, rabbits, and mice using subcutaneous, topical dermal, and oral administration. Developmental or teratogenic effects were observed in all animals (rats, mice, and rabbits) treated with dosages of mometasone furoate between 15-2800 mcg/kg.[2]

X*** Carcinogenicity of Mometasone Furoate

Inhalation studies ranging from 19 months to 2 years with mometasone furoate in mice and rats did not produce statistically significant increases in tumor formation at doses of 67 and 160 mcg MF/day respectively. [2] Mometasone furoate is not considered to be a carcinogen by IARC, ACGIH, NTP, or OSHA.

X*[a] Sensitization potential of Mometasone Furoate: No sensitization reaction known for Mometasone Furoate.

3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE)

For the Dermal PDE

PDE Value (Topical) (Lowest)	LOAEL/NOAEL	Repeat-dose toxicity
3 µg/ person /day	150 µg/Kg/day	For dermal PDE (PDE $_{dermal}$), the most sensitive indicator of an adverse effect of topically applied mometasone in rabbits includes multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 µg/kg and above). [4]

Adjustment Factor	Value	Justification
F1: Extrapolation between species (2-12)	2.5	For extrapolation from rabbit to human.
F2: Inter-individual variability (10)	10	The default value for the inert-individual variation.
F3: Toxicological study chronic or acute (1-10). Not included genotoxicity, carcinogenicity, neurotoxicity and teratogenicity	1	Because the treatment with mometasone spanned the whole period of organogenesis.
F4: for severe toxicity (1-10)	10	Because severe toxicity (teratogenicity) was observed.
F5: NOAEL vs LOAEL (10 if LOAEL)	10	Because the LOAEL was used for the PDE derivation.
PK Correction	NA	Because the oral PDE value was derived based on study using the oral route of administration, which is the intended clinical route of administration for mometasone Furoate.

For the inhalational PDE

PDE Value (Inhalational) (Lowest)	LOAEL/NOAEL	Repeat-dose toxicity
18 µg/person/day	0.13 ug/L [equivalent to 88.71 µg/kg/day]. [8]	Inhalation study in rats (Rat, Inhalation, 90 d, daily) revealed that the most sensitive indicators of adverse effects seen in non-clinical toxicity study were reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver. The NOAEL for these effects was 0.13 ug/l. [6]

Adjustment Factor	Value	Justification
F1: Extrapolation between species (2-12)	5	For extrapolation from rats to humans.
F2: Inter-individual variability (10)	10	To account for variability between individuals.
F3: Toxicological study chronic or acute (1-10). Not included genotoxicity, carcinogenicity, neurotoxicity and teratogenicity	5	Because the study duration was 3-month in rats.
F4: for severe toxicity (1-10)	1	Because no sever toxicity was observed.
F5: NOAEL vs LOAEL (10 if LOAEL)	1	Because the NOAEL was used for PDE derivation.
PK Correction	N/A	Because the PDE value was derived based on study using the inhalation route of administration, which is the intended clinical route of administration for Mometasone Furoate inhaler

Occupational Exposure Limits (OEL) for Mometasone Furoate

$$\text{OEL (mg/m3)} = \frac{\text{PoD} \times \text{BW}}{\text{UFC} \times \text{TK} \times \text{V}} \quad \text{or} \quad \frac{\text{Inhalational PDE (mg/person/day)}}{\text{TK} \times \text{V}}$$

$$\text{OEL (mg/m3)} = \frac{18\ \mu\text{g/ person/day}}{1 \times 10} = \underline{\mathbf{1.8\ \mu g/m^3}}\ \mathbf{(OEB\ 3)}$$

Where: -

OEL = Occupational Exposure Limit

PoD = Point of Departure for Extrapolation (mg/kg − day)

BW = Body Weight (kg)

UFC= Composite Uncertainty Factor

PDE =Permitted daily exposure

TK = Toxicokinetic adjustment = 1; because the no information regarding inhalational bioavailability of Mometasone Furoate and thus, it is assumed to be 100 %.

V = Volume of air breathed during work shift (m3) =10 m^3/work shift

Expiration Date: Risk Assessment:

A risk assessment has been performed following the ICHQ9 "*Quality Risk Management*" to establish the expiration periods for the PDE reports considering the associated risk. The criteria for the assessment are described below:

Risk Factor	Value	Characteristics
EMA *List of medicines under additional monitoring EMA/245297/2013 Rev.140**	1	Not present
	2	Present*
PDE value	1	Higher than 1µg/day
	2	Equal/Lower than 1µg/day
	2	PDE = TTC

**The substance appears in the EMA list (EMA/245297/2013 Rev.140*) alone or in combination.*

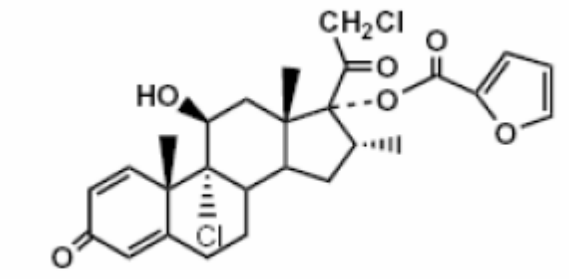
Considering these criteria, the **Risk Priority Number (RPN)**, which establishes the expiration date for each document, is calculated as follows:

Risk	Assessment
Low (2)	Expired in 5 years
High (3-4)	Expired in 3 years

Mometasone Furoate is not among EMA *List of medicines under additional monitoring EMA/245297/2013 Rev.140*, and the lowest dermal PDE value is* 3µg/person/day. *Thus, RPN for Mometasone Furoate = 2, and thus the expiration date of the risk assessment report is 5 year.*

Risk Factor	Value	Characteristics
EMA *List of medicines under additional monitoring EMA/245297/2013 Rev.140**	1	Not present
Dermal PDE value	1	Higher than 1µg/day (3 µg/person/day)
Risk Priority Number (RPN)	2	Low
Report expiration	5-year	Report expired in 5-year

4. IDENTITY OF THE ACTIVE SUBSTANCE

Common Name	Mometasone Furoate
Chemical Name	83919-23-7
CAS Registry Number	[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]furan-2-carboxylate
Molecular formula	$C_{27}H_{30}Cl_2O_6$
Molecular weight	521.4 g/mol g/mol
Structural formula	

a) Indication of Mometasone Furoate

There are 3 formulations of mometasone furoate with various indications. The inhaler is indicated for prophylaxis of asthma in patients ≥4 years. The nasal spray is indicated for treating nasal symptoms of allergic rhinitis in patients ≥2 years, treating symptoms of nasal congestion from seasonal allergic rhinitis in patients ≥2 years, treating nasal polyps in patients ≥18 years, and prophylaxis of seasonal allergic rhinitis in patients ≥12 years. The ointment is indicated for symptomatic treatment of dermatitis and pruritis in patients ≥2 years. [12]

b) Mechanism of Action of Mometasone Furoate

Mometasone furoate is a corticosteroid demonstrating potent antiinflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown. Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Maximum improvement in symptoms following inhaled administration of mometasone furoate may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

c) Pharmacodynamics of Mometasone Furoate

Mometasone is a synthetic corticosteroid with an affinity for glucocorticoid receptors 22 times higher than that of dexamethasone. Mometasone furoate also has a lower affinity to mineralocorticoid receptors than natural corticosteroids, making it more selective in its action. Mometasone furoate diffuses across cell membranes to activate pathways responsible for reducing inflammation. [12]

d) GHS Classification Criteria for Mometasone Furoate Acute Toxicity: - [1,10,11;13]

Acute oral toxicity:	Category 5
Acute dermal toxicity:	No data available
Acute Inhalation toxicity:	No data available
Acute aquatic toxicity:	No data available
Chronic aquatic toxicity:	Category 2
Skin Corrosion/irritation:	Category 2
Skin sensitization:	Based on available data, the classification criteria are not met
Serious Eye Damage/Eye Irritation:	Category 2
Respiratory sensitization:	No data available
STOT-SE, respiratory tract irritation:	Category 3
STOT-RE	Category 1: (endocrine system)
Germ cell mutagenicity:	Based on available data, the classification criteria are not met.
Reproductive toxicity:	Category 1A

e) Acute single dose toxicity studies of Mometasone Furoate

The acute subcutaneous LD50 values of mometasone furoate were determined to be between 200 and 2000 mg/kg in mice, 2000 mg/kg or greater in rats and >200 mg/kg in dogs. Following oral administration the LD50 values were >2000 mg/kg in mice and rats. As expected, the LD50 values for young (21-day old) mice and rats were 2 to 20 times lower than those for adult animals.

Summary of acute single dose toxicity of Mometasone furoate :- [1,14]

Acute toxicity

Species	Route of application	LD_{50} [mg/kg]
Mouse	Subcutaneous	200-2,000
Rat	Subcutaneous	2,000
Dog	Subcutaneous	>200
Mouse	Oral	>2,000
Rat	Oral	>2,000

f) Repeated dose toxicity studies of Mometasone Furoate

Several repeat dose studies have been performed with mometasone furoate (MF) using rodents and dogs. The systemic effects observed after treatment with MF are fairly consistent across species and exposure routes. [2]

One-month oral toxicity studies in rats and dogs showed changes in the thymus, mesenteric lymph nodes, liver, adrenals, and skin with a reported NOEL of 5 mcg/kg in rats and LOEL of 500 mcg/kg in dogs. [2]

Short- and long-term inhalation studies in rats, mice and dogs were performed using doses of MF ranging from 0.02 mcg/L to 16 mcg/L. Common clinical signs observed across species included changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidney, and liver. [2]

Following repeated administration of mometasone furoate in rats, rabbits and dogs at doses up to 670 times the anticipated maximum human dose for up to 6 months; findings were typical of corticosteroid administration in all species. These included (1) slight reduction in body weight gain, (2) skeletal muscle wasting, (3) abdominal distention, (4) decrease in lymphocytes and eosinophils and increase in neutrophils, (5) increase in serum transaminases (SGPT and SGOT), cholesterol and triglycerides, (6) lipemia, and (7) organ changes (atrophy of spleen and thymus, local skin thinning, increased liver and kidney weights and reduced osteogenesis). These changes were generally observed more frequently or more severe in animals receiving the comparative agent, betamethasone valerate. No unusual systemic effects were observed with either drug. Dermal responses to repeated application of mometasone furoate or betamethasone valerate cream were limited to transient episodes of slight to moderate erythema, skin wrinkling, desquamation and the presence of papules and/or pustules. In reproduction studies, mometasone furoate produced effects which are known to be associated with corticosteroids and/or progestational agents such as reduced maternal body weight gain, suppression of fetal growth, delayed ossification, umbilical hernias, prolonged gestation, difficult and prolonged labor and inability to deliver. [15]

5. OBJECTIVE AND SEARCH STRATEGY

In accordance with the "Guideline on setting health-based exposure limits for use in risk identification in the of health-based exposure limits for a residual active substance is based on the calculation of the manufacture of different medicinal products in shared facilities" (EMA/CHMP/CVMP/SWP/169430/2012) the determination Permitted Daily Exposure (PDE). Determination of a PDE involves (i) hazard identification by reviewing all relevant data, (ii) identification of "critical effects", (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects, and (iv) use of several adjustment factors to account for various uncertainties.

The NOAEL/LOEL value has been used to calculate a PDE in this study.

The purpose of this document is to provide a brief summary of the scientific information relative to Mometasone Furoate compound.

All the information presented in this document is fully based on published data. With this aim, several pharmaceutical and medical databases were scanned to reduce the risk of some reports missing. They include databases such as DrugBank Database; DailyMed Database; PubChem Database; FDA drug approval data base; European Medicines Agency database; Australian Register of Therapeutic Goods (ARTG), PubMed - National Institutes of Health (NIH), Aggregated Computational Toxicology Online Resource (ACToR), Toxicity Reference Database (ToxRefDB); Aggregated Computational Toxicology Online Resource (ACToR) (see the reference section)

6. HAZARD IDENTIFICATION

a) Pharmacodynamics data

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. In a study to examine the relative potency of ligand-induced gene activation of the glucocorticoid responsive elements, mometasone furoate was the most potent glucocorticoid in activating the glucocorticoid receptor with an activity approximately 46x that of dexamethasone, 23x that of triamcinolone acetonide, 13x that of budesonide and 1.8x that of fluticasone.

In cell culture, mometasone furoate was shown to be at least ten times more potent than other steroids, including beclomethasone dipropionate (BDP), betamethasone, hydrocortisone and dexamethasone, at inhibiting the synthesis/release of IL-1, IL-6 and TNFα. Mometasone furoate (IC50=0.12 nM) was also at least six times more potent than BDP and betamethasone at inhibiting IL-5 production.

Mometasone furoate was more potent than budesonide, beclomethasone dipropionate, triamcinolone acetonide and hydrocortisone acetate at inhibiting basophil histamine release (IC50=0.3 nM) and reducing eosinophil survival (IC50=0.7 nM).
In a preclinical model, the compound has been shown to reduce the accumulation of eosinophils markedly at the site of an allergic reaction. In allergic mice with IgE-mediated allergy, inhaled mometasone furoate at doses as low as 13 mcg/kg inhibited eosinophil infiltration into bronchoalveolar lavage fluid and the lung bronchi and bronchioles.
Additionally, mometasone furoate reduced the number of lymphocytes, and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

Mometasone furoate demonstrated no mineralocorticoid, androgenic, antiandrogenic, or estrogenic activity but like other glucocorticoids, demonstrated progesterone-like activities in preclinical studies. The ratio of glucocorticoid to progesterone receptor activation for mometasone furoate was comparable to other glucocorticoids studied. However, the clinical significance of these findings in relation to minimally detectable plasma concentrations of mometasone furoate when administered via dry powder inhaler at recommended doses is unknown. After administration of a single inhaled dose of mometasone furoate to adult male rats, the highest drug levels were seen in the esophagus, airways, and mouth. [4]

b) Acute toxicity

Two acute inhalation toxicity studies were conducted in mice (i.e., 4-hr whole-body exposure to micronized, pure, mometasone furoate powder). In the first study, the mean estimated doses were 582 mg/kg (in mice) and 394 mg/kg (for rats), assuming 100% deposition. No clinical signs were observed in either species during the 36-day post-exposure observation period. However, lower body weights compared to pretreatment values were observed in both species. In the second study, rats were exposed by whole body exposure to 0.68 mg/L micronized mometasone furoate powder for 4 hours, and then observed for 3 weeks. Weight loss occurred during the observation period; while rales, ano-genital staining, soft stools and emaciation were the principal clinical observations. At necropsy, several rats had discolored lungs, small spleens and discolored brown skin. [5]

Mometasone Furoate

LD50 (Oral); Rat: > 2,000 mg/kg No mortality observed.
LD50 (subcutaneous): Rat: 300 mg/kg

c) Repeated dose toxicity

Systemic absorption of topical corticosteroids can produce reversible hypothalamic pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Two-week, one-month, three-month, six-month and one-year (dog only) studies were conducted in rats and dogs with the lactose containing mometasone furoate dry powder inhaler. No unexpected (non-glucocorticoid related) effects were observed at any dose in any of the studies. Mometasone furoate:lactose powder agglomerate (1:19) was well-tolerated when administered by nose-only inhalation to rats one hour daily for two weeks at target exposure concentrations of 0.13, 0.50 or 2.0 mcg/L. Based on organ weight changes and histopathology findings, the target organs for inhaled mometasone furoate (lactose formulation) were trachea (globule leukocytes), spleen, thymus and bone marrow of both males and females, and mammary gland of females. Glucocorticoid activity was shown as lymphoid depletion accompanied by lympholysis of the thymus in males and females. Progestational-like changes were enhanced lobuloalveolar development and secretion in mammary glands of females at the high dose level. [5]

Mometasone furoate:lactose powder agglomerate (1:5.8 or 1:19) was well-tolerated when administered by nose-only inhalation to male and female rats one hour daily for one month at exposure concentrations of 0.13, 0.50, or 2.0 mcg/L. Based on organ weight changes and histopathology findings, the target organs for inhaled MF were lymph nodes, thymus, trachea (globule leukocytes) and, in females, bone marrow, mammary gland, and reproductive tract. Glucocorticoid activity was shown as lymphoid depletion accompanied by lympholysis of the thymus in males and females. Progestational-like changes were enhanced lobuloalveolar development and secretion in mammary glands of females. [5]

Mometasone furoate:lactose powder agglomerate (1:19) was also well-tolerated when administered by nose-only inhalation to rats one hour daily for three months at exposure concentrations of 0.13, 0.50 or 2.0 mcg/L. Based on organ weight changes and histopathology findings, the target organs were trachea (globule leukocytes), thymus, lymph nodes and, in females, mammary gland. Glucocorticoid activity was shown as lymphoid depletion accompanied by lympholysis of the thymus and lymphoid depletion in mesenteric lymph nodes. Progestational-like changes were as observed in the one month study. Thymic, lymphoid and progestational-like changes were reversed following a 4-week recovery period. [5]

Mometasone furoate:lactose powder agglomerate (1:5.8) was well-tolerated when administered by nose-only inhalation to male and female rats one hour daily for six months at exposure concentrations of 0.13, 0.50, or 2.0 mcg/L. Based on organ weight changes and histopathological findings, the target tissues for inhaled MF were lymphoid tissues, thymus, tracheal epithelium (globule leukocytes), hair follicles, and, in females, mammary gland and reproductive tract. Glucocorticoid activity was observed as lymphoid depletion of the thymus in males and females at 0.50 mcg/L and 2.0 mcg/L exposures, respectively. Progestational-like changes were similar to those observed in the previous studies. [5]

Daily administration of mometasone furoate:lactose (1:19) powder agglomerate by mouth-only inhalation to beagle dogs for 30 minutes per day for 14 days at concentrations of 1, 4 and 16 mcg/L was well tolerated. Organ weight changes and histopathologic changes were observed in the thymus, spleen, gut-associated lymphoid tissue and peripheral lymph nodes. A no-effect dose for glucocorticoid effects was not identified. The no-effect dose for progestational effects was >16 mcg/L. [5]

Daily administration of mometasone furoate:lactose powder agglomerates by mouth-only inhalation to beagle dogs for 30 minutes per day for 28 days at aerosol concentrations of 0.1, 0.5, 4.0 (1:5.8), and 4.0

(1:19) mcg/L was also well tolerated. Adrenal atrophy was observed at the high-dose (4.0 mcg/L), with reduced absolute and relative weights and vacuolization of the zona fasciculate in females exposed to 0.5 mcg/L and in males and females in the high-dose groups (4.0 mcg/L). There was a minimal increase in bone marrow adipose tissue of the 4.0 mcg/L males and females. The no-effect dose for glucocorticoid effects in this study was 0.1 mcg/L (1:5.8). The no-effect dose for progestational activity was 4.0 mcg/L. [5]
Daily administration of mometasone furoate:lactose (1:19) powder agglomerate by mouth-only inhalation to beagle dogs for 30 minutes per day for 13 weeks at concentrations of 0.1, 0.5, or 4.0 mcg/L was well tolerated. No unexpected effects were seen at any dose. Target organs for this inhaled MF lactose formulation were the adrenal gland, thymus and gut-associated lymphoid tissue and various lymph nodes. The no-effect dose for glucocorticoid activity was 0.1 mcg/L. The no-effect dose for progestational effects was >4.0 mcg/L. [5]

Beagle dogs were administered mometasone furoate:lactose agglomerates (1:5.8) by mouth-only inhalation for 30 minutes per day for 6 months at concentrations of 0.1, 0.5, and 4.0 mcg/L. Target organs were the adrenal glands, liver, and lymph nodes. The no-effect dose for glucocorticoid activity was 0.1 mcg/L on the basis of minimal effects on cholesterol levels at an exposure concentration of 0.5 mcg/L. The no-effect dose for progestational effects was >4.0 mcg/L. [5]

Daily administration of mometasone furoate:lactose agglomerate (1:5.8) by mouth-only administration to beagle dogs for 30 minutes per day for 12 months at concentrations of 0.1, 0.5, and 4.0 mcg/L was well tolerated. Target organs were the adrenal glands of both sexes and reproductive organs in females based on histopathologic changes. The no-effect exposure concentration for MF:lactose agglomerate was 0.5 mcg/L. The no-effect concentration for progestational activity was >4.0 mcg/L. There were no lactose-related findings in this study. [5]

For mometasone furoate, it was concluded that the toxicity profile was typical of dose-related glucocorticoid effects. Target organs were thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy in rats and dogs. The lowest NOAEL reported was 1.25µg/kg bw/day, obtained from 13-week oral study in rats. [13]

Based on this information, the lifetime oral PDE value for Mometasone Furoate-induced critical effect "toxicity to thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy" in rats can be calculated in accordance with ICH Q3C guideline Appendix (3) [9] using the following equation: -

Lifetime PDE = NOAEL x body weight adjustment/F1*F2*F3*F4*F5
Lifetime PDE = 1.25µg/kg/day x 50 kg/5 x10 x 5 x 1x 1 = 250 ng/person/day
The values of the uncertainty factors used in this equation was as follow:
F1 = 5; for extrapolation from rats to humans
F2 = 10; to account for variability between individuals
F3 =5; because the study duration was 13-week in rats
F4 = 1; because there no severe toxicity was observed
F5 = 1; because the NOAEL was used for PDE derivation

Summary of repeated dose toxicity of Mometasone Furoate:- [6]

- NOAEL (Rat, Oral, 30 d, daily): 5 ug/kg (Target Organ(s): thymus, lymph nodes, liver, adrenal gland, skin)
- LOAEL (Dog, Oral, 30 d, daily): 500 ug/kg (Target Organ(s): thymus, lymph nodes, liver, adrenal gland, skin)

- NOAEL (Rat, Inhalation, 90 d, daily): 0.13 ug/l The systemic effects observed are typical of corticosteroids as a class and include reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver.

- NOAEL (Dog, Inhalation, 90 d, daily): 0.5 ug/l The systemic effects observed are typical of corticosteroids as a class and include reversible changes in body weights, adrenalcglands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver.

Thus, the daily dose is = 0.13 µg/L x 290 L/0.425kg = 88.71 µg/kg/day. [8]
Rat respiratory volume: 290 L/ day [8]
Rat body weight: 0.425 kg. [8]

Based on this information, the lifetime inhalation PDE value for Mometasone Furoate -induced critical effect "reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver" in rats can be calculated in accordance with ICH Q3C guideline Appendix (3) [9] using the following equation: -
Lifetime inhalation PDE = LOAEL x body weight adjustment/F1*F2*F3*F4*F5
Lifetime inhalation PDE = 88.71 µg/kg/day x 50 kg/5 x10 x 5 x 1x 1= **18 µg/person/day**
The values of the uncertainty factors used in this equation was as follow:
F1 = 5; for extrapolation from rats to humans
F2 = 10; to account for variability between individuals
F3 = 5; for short duration of study in rats (3-month duration)
F4 = 1; because there no severe toxicity was encountered
F5 = 1; because the NOAEL was used for PDE derivation

d) Carcinogenicity

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis and -2 times- the maximum recommended daily inhalation dose in pediatric patients based on a mcg/m^2 basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis and 2 times the maximum recommended daily inhalation dose in pediatric patients based on a mcg/m^2 basis). [4]

e) In vitro / in vivo genotoxicity studies

Mometasone furoate was non-mutagenic in the mouse-lymphoma assay and the Salmonella/*E. coli*/mammalian microsome mutagenicity bioassay. At cytotoxic doses only, mometasone furoate produced an increase in chromosome aberrations *in vitro* in Chinese hamster ovary cell (CHO) cultures in the non-activation phase, but not in the presence of rat liver S9 fraction. However, mometasone furoate did not induce chromosomal aberrations *in vitro* in a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, or *in vivo* in the mouse bone marrow erythrocyte-micronucleus assay, in the rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes. The finding of simple chromosomal aberrations in the non-activation phase of the CHO assay is considered to be related to cytotoxicity and is not considered to be of significance in the risk assessment of mometasone furoate because of the negative results in the S9 phase of this assay, the negative results in a second *in vitro* chromal aberrations assay (CHL assay), and the negative results in three *in vivo* chromosomal aberrations assays. [4]

f) Reproductive and developmental toxicity:- [4]

In mice, mometasone furoate caused cleft palate at subcutaneous doses ≥ 60 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m2 basis). Fetal survival was reduced at 180mcg/kg, approximately equal to the maximum recommended daily inhalation dose in adults on a mcg/m2 basis. No toxicity was observed at 20mcg/kg. {this dose is considered as NOAEL}

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600mcg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on a mcg/m2 basis). A dose of 300mcg/kg produced delays in ossification, but no malformations.
When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15mcg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5mcg/kg.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700mcg/kg. At 2800 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg.

Corticosteroids are known teratogens in rodent species with some teratogenic effects having been observed in non-human primates. They are generally teratogenic in laboratory animals when administered systemically at low dosages. Developmental toxicity studies were conducted with mometasone furoate in rats, rabbits, and mice using subcutaneous, topical dermal, and oral administration. Developmental or teratogenic effects were observed in all animals (rats, mice, and rabbits) treated with dosages of mometasone furoate between 15-2800 mcg/kg. [2]

Mometasone furoate (MF) caused cleft palate in mice given subcutaneous doses of greater than or equal to 60 mcg/kg. Offspring survival was reduced when mice were treated with 180 mcg/kg (NOEL 20 mcg/kg). No effect on fertility in rats was seen following subcutanteous administration of doses up to 15 mcg MF/kg; however, prolonged gestation, prolonged and difficult labor, reduced offspring survival and reduced maternal body weight gain were observed at 15 mcg MF/kg. Similar effects were seen in rabbits and rats following topical dermal doses of greater than or equal to 150 mcg MF/kg including: reductions in maternal body weight gain, cleft lip/palate, protruding bowel, brain and umbilical hernias and effects on fetal growth (lower fetal body weights and/or delayed ossification). Oral doses of 700 mcg MF/kg in rabbits

caused increased incidences of resorptions, cleft palate and head malformations. Following oral doses of 2800 mcg MF/kg, rabbits failed to become pregnant (resorptions). [2]

Based on this information, the lifetime dermal PDE value for mometasone furoate-induced critical effect "multiple malformations including flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) " in rabbits can be calculated in accordance with ICH Q3C guideline Appendix (3) [9] using the following equation: -

Lifetime dermal PDE = LOAEL x body weight adjustment/F1*F2*F3*F4*F5
Lifetime dermal PDE = 150µg/kg/day x 50 kg/2.5 x10 x 1 x 10x 10 = 3 µg/person/day
The values of the uncertainty factors used in this equation was as follow:
F1 = 2.5, for extrapolation from rabbits to humans
F2 = 10; to account for variability between individuals
F3 =1; because treatment with mometasone furoate was spanning the whole period of organogenesis
F4 = 10; because severe toxicity (teratogenicity) was encountered
F5 = 10; because the LOAEL was used for PDE derivation

7. IDENTIFICATION OF CRITICAL EFFECTS

a) Most sensitive indicator of an adverse effect seen in non-clinical toxicity data

The most sensitive indicator of an adverse effect of topically applied mometasone in rabbits includes multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above). [4]

For inhalational mometasone; the most sensitive adverse effects include reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver" in rats. [4]

For oral mometasone, the most sensitive adverse effects include toxicity to thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy. [13]

b) Clinical therapeutic and adverse effects

The side effect of mometasone furoate ointment include:- burning, itching, irritation, redness, or dryness of the skin; acne; skin sores; tiny red bumps or rash around the mouth; small white or red bumps on the skin; bruising or shiny skin; changes in skin color.

8. RATIONALE FOR (NOAEL) VALUES SELECTION

The Lowest LOAEL/NOAEL for the most sensitive and clinically relevant critical effect of Mometasone was used for the PDE derivation.

For the dermal PDE (PDE dermal); the most sensitive critical effect was multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above.[4] Thus, the lowest LOAEL value is considered to be 150µg/kg/day and was used for the PDE derivation.

For the inhalational mometasone furoate, the most sensitive critical effect was toxicity to the target organs including reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver. The NOAEL for these effects was 0.13 ug/l. [6]

9. RATIONALE FOR SELECTION OF ADJUSTMENT FACTORS

For dermal PDE (PDE $_{dermal}$), the most sensitive indicator of an adverse effect of topically applied mometasone in rabbits includes multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above). [4]

Based on this information, the lifetime dermal PDE value for mometasone furoate-induced critical effect "multiple malformations including flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) " in rabbits can be calculated in accordance with ICH Q3C guideline Appendix (3) [9] using the following equation: -

Lifetime dermal PDE = LOAEL x body weight adjustment/F1*F2*F3*F4*F5

Lifetime dermal PDE = 150µg/kg/day x 50 kg/2.5 x10 x 1 x 10x 10 = 3 µg/person/day

The values of the uncertainty factors used in this equation was as follow:

F1-Interspecies differences = 2.5, for extrapolation from rabbits to humans

F2-Intra-species variation = 10; to account for variability between individuals

F3-Duration of exposure =1; because treatment with mometasone furoate was spanning the whole period of organogenesis

F4-Nature of toxicity = 10; because severe toxicity (teratogenicity) was encountered

F5-NOAEL to LOAEL = 10; because the LOAEL was used for PDE derivation

For inhalational PDE (PDE $_{inhalation}$):-

For the inhalational mometasone furoate, the most sensitive critical effect was toxicity to the target organs including reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver. The NOAEL for these effects was 0.13 ug/l. [6]

Thus, the daily dose is = 0.13 µg/L x 290 L/0.425kg = 88.71 µg/kg/day. [8]

Rat respiratory volume: 290 L/ day [8]

Rat body weight: 0.425 kg. [8]

Based on this information, the lifetime inhalation PDE value for Mometasone Furoate -induced critical effect "reversible changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidneys and liver" in rats can be calculated in accordance with ICH Q3C guideline Appendix (3) [9] using the following equation: -

Lifetime inhalation PDE = LOAEL x body weight adjustment/F1*F2*F3*F4*F5

Lifetime inhalation PDE = 88.71 µg/kg/day x 50 kg/5 x10 x 5 x 1x 1= **17.75 µg/person/day**

The values of the uncertainty factors used in this equation was as follow:

F1-Interspecies differences = 5; for extrapolation from rats to humans

F2-Intra-species variation = 10; to account for variability between individuals

F3-Duration of exposure = 5; for short duration of study in rats (3-month duration)

F4-Nature of toxicity = 1; because there no severe toxicity was encountered

F5-NOAEL to LOAEL = 1; because the NOAEL was used for PDE derivation

10. PK CORRECTION

N/A

Because the dermal PDE value was derived based on study using the dermal route of administration, while the inhalational PDE was derived based on a study using the inhalational route of administration.

11. REFERENCES

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10. Material safety data sheet for Mometasone Furoate issued by Cayman Chemical Company
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12-ANNEX 1: PHARMACOKINETICS AND METABOLISM

The pharmacokinetic properties of Mometasone Furoate:- [2,4]

Absorption : Following inhalation of 1000 mcg of tritiated mometasone furoate inhalation powder by 6 healthy human subjects, systemic exposure to mometasone furoate was low. Following an inhaled single 400 mcg dose of mometasone furoate by 24 healthy subjects, plasma concentrations for most subjects were near or below the lower quantitation limit (LOQ) for the assay (50 pcg/mL). However, when a new, more sensitive assay with a 200-fold lower LOQ of 0.25 pcg/mL was used, inhalation of mometasone resulted in quantifiable plasma concentrations in all subjects. The estimates of the mean absolute bioavailability of 400 mcg mometasone furoate inhaled from the mometasone were 16% for healthy volunteers and 10% for asthmatics. Following administration of a 400 mcg dose twice daily for 28 days, concentration-time profiles were discernible, but with large inter-subject variability.

Distribution: Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean terminal half-life of about 5 hours and the mean steady-state volume of distribution of 152 L. The in vitro protein binding for mometasone furoate was reported to be 98% to 99% (in a concentration range of 5-500 ng/mL).

Biotransformation: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In vitro studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound; however, no major metabolites were identified.

Elimination: Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine.

Geriatrics: A trial of geriatric patients showed no difference in safety or efficacy compared to younger patients, however patients of an even greater age may still be more sensitive to mometasone furoate. [12]

Renal Insufficiency: The effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated.

Hepatic Insufficiency: Administration of a single inhaled dose of 400 mcg of mometasone to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only one or two subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.

13-ANNEX 2: GLOSSARY

ADI: Acceptable daily intake
AUC: Area under the curve
GRAS: Generally regarded as safe
GLP: Good laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
LED: Lowest-effective dose
LDLo (Lethal Low Dose): Lowest lethal dose
TDLo (Toxic Dose Low,): Lowest published toxic dose LOAEL: Lowest-observed-adverse-effect level
LOEL: Lowest-observed-effect level
MSDS: Material safety data sheet
MTD: Maximum tolerable dose
MPDD: Maximum permissible daily dose
MTEL: Maximum tolerable exposure level
NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect level
OEL: Occupational exposure limit
QSAR: Quantitative structure–activity relationship SDS: Safety data sheet

14. HISTORY OF CHANGES

Version	Issue Date	Reason
1.0	**09/03/2026**	**First Issue**

