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APPLICATION NUMBER:

205434Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205-434
Supporting document/s: S000
Applicant's letter date: September 23, 2013
CDER stamp date: September 23, 2013 (eCTD format)
Product: Flonase® Allergy Relief (fluticasone propionate nasal spray, 50 µg)
Indication: Allergy symptom relief
Applicant: GlaxoSmithKline Consumer Healthcare
Review Division: DNCE
Primary Reviewer: Wafa Harrouk, Ph.D.
Secondary Reviewer: Paul Brown, Ph.D.
Division Director: Theresa Michele, M.D.
Project Manager: Jung Lee, Pharm. D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-434 are owned by GSKCH for which the above mentioned sponsor has obtained a written right of reference.

Any information or data necessary for approval of NDA 205-434 that the sponsor does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 205-434.

Executive Summary

This fully electronic¹ New Drug Application (NDA 205-434) has been submitted by GlaxoSmithKline Consumer Healthcare (GSK CH) to obtain marketing approval for the over the counter (OTC) use of Flonase[®] (fluticasone propionate nasal spray, 50 µg) in the management of the symptoms of allergic (b) (4) rhinitis in adults 18 years and older. The sponsor is seeking approval for the use of *Flonase Allergy Relief* for the temporary relief of the following symptoms due hay fever, other respiratory allergies (b) (4)

(b) (4)

(b) (4) nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes. The watery eye claim was not included in the original Flonase approval but has been evaluated in clinical studies conducted for this NDA. No new nonclinical studies were conducted for this NDA.

RECOMMENDATIONS

Approvability: No Pharmacology/Toxicology issues were identified for this NDA. This NDA can be approved from the pharm/tox perspective.

Comments to be conveyed to the sponsor: None

Overview & Regulatory History

Flonase was originally approved by the U.S. Food and Drug Administration (FDA) on October 19, 1994 as a prescription-only treatment for the management of the nasal symptoms of seasonal (SAR) and perennial (PAR) allergic rhinitis in adults and adolescents 12 years of age and older. The proposed OTC product, referred to in this NDA as *Flonase Allergy Relief*, is identical in composition to the current Rx Flonase product. GSK CH is seeking approval for the use of *Flonase Allergy Relief* for the temporary relief of allergy symptoms such as nasal congestion, runny nose, sneezing,

itchy nose, and itchy, watery eyes. The efficacy of Flonase in relieving ocular symptoms associated with allergic rhinitis had not been previously established. The sponsor conducted three clinical studies to evaluate relief of ocular symptoms associated with allergic rhinitis².

Subsequent approvals for Rx Flonase to expand the indication include:

- 31-Oct-1997: Approved for use in pediatric patients 4 years of age and older;
- 11-Dec-1998: Approved for use in patients with perennial non-allergic rhinitis (PNAR);
- 23-May- 2002: Approved for as-needed use.

DRUG INFORMATION

Relevant INDs, NDAs, BLAs and DMFs

GSKCH submitted a letter providing the right of reference to the following IND/NDAs:

NDA 020-121 FLONASE Nasal spray, 50 µg

NDA 022-051 VERAMYST Nasal spray 27.5 µg

IND 028636 Fluticasone Propionate aqueous nasal spray

The following DMFs were also cross referenced: DMF (b) (4), DMF (b) (4) and DMF (b) (4).

Drug Formulation

Flonase allergy relief nasal spray, 50 µg is exactly the same in composition as the approved Rx Flonase® Nasal Spray, 50 µg. It is a white, (b) (4) suspension of (b) (4) fluticasone propionate (b) (4) for topical administration to the nasal mucosa by means of a metering, atomizing spray pump (same one used for the Rx product).

¹ This NDA was submitted in accordance with the electronic Common Technical Document (eCTD)

² Clinical trials conducted for this NDA are study #'s: 30033, 30034, and RH01619

Batch Formula for Flonase Allergy Relief Nasal Spray, 50 mcg

Component	Quantity/ (b) (4) Batch	% w/w
Fluticasone Propionate ^a	(b) (4)	
Dextrose (b) (4)		
Microcrystalline Cellulose and Carboxymethylcellulose Sodium (b) (4)		
Phenylethyl Alcohol		
Benzalkonium Chloride (b) (4)		
Polysorbate 80		
Purified Water		
(b) (4)		

Dosing

The recommended dosage for Fluticasone Propionate (b) (4) Nasal Spray in adults and children over 12 years of age is two sprays into each nostril once daily, (b) (4)

(b) (4)

(b) (4) For children 4 to 11 years of age, the recommended dosage is one spray into each nostril once daily, (b) (4)

(b) (4)

(b) (4)

NONCLINICAL SUMMARY

No new nonclinical pharmacology or toxicology data were conducted for this Rx to OTC switch application. Module 4 for nonclinical data was not included in this submission. The nonclinical information was included in the common technical summary section of the submission which is summarized below.

Pharmacokinetics

The nonclinical pharmacokinetic (PK) profile of fluticasone propionate has been investigated in the mouse, rat and dog using intravenous, subcutaneous and oral routes

of administration. No PK studies have been conducted using the intranasal route of administration for Fluticasone Propionate. Following intravenous administration, plasma concentration-time curves in rats and dogs showed the majority of fluticasone propionate was rapidly eliminated from plasma, with a half-life of 0.65 hours in the rat and 1.4 hours in the dog. Less than 10% of the dose, which was associated with adipose tissue, was eliminated more slowly, with a half-life of 4 hours in the rat and 10 hours in the dog. High clearance via the hepatic metabolism resulted in an almost nil oral bioavailability for fluticasone propionate in rats and dogs. Data on plasma levels of fluticasone propionate from repeat-dose inhalation toxicity studies in rats and dogs indicate that systemic exposure increased with increasing dose. The major route of metabolism for fluticasone propionate is hydrolysis of the S-fluoromethyl carbothioate group to yield the carboxylic acid metabolite, GR36264. This metabolite was the major constituent detected in biliary and fecal radioactivity in the rat and it was also detected in significant quantities in the feces of mice following oral and subcutaneous administration of fluticasone propionate. In all animal species, the majority of fluticasone propionate was excreted in the feces within 48 hours after dosing. Renal clearance is of minor importance since urinary excretion accounted for less than 5% of a parenteral dose and only traces of unchanged drug were excreted in the urine.

Acute Toxicity Studies

The acute toxicity profile of fluticasone propionate was evaluated in mice, rats and dogs following oral, subcutaneous, intravenous, and inhalation exposure.

High oral doses of fluticasone propionate (up to 1000 mg/kg) were well tolerated by mice and rats. Following 3 days of dosing, the only adverse effect that was observed in treated animals was a slowing in growth rate and histological evidence of cortical depletion of the thymus. These effects were reversible as evidenced by their absence in animals evaluated 14 days after the end of dosing. Acute inhalation of fluticasone propionate at doses of 1.66 mg/kg in the rat and 0.82 mg/kg in the dog produced no biologically significant effects.

Repeat Dose Toxicity Studies

Long term oral toxicity studies of up to 26 weeks duration were conducted with fluticasone propionate in rats and dogs. In these studies, the effects observed were consistent with the administration of a potent glucocorticoid drug.

Subcutaneous repeated-dose toxicity studies in the rat were conducted with fluticasone propionate in rats and in dogs. High doses used in the dog study produced classical symptoms of steroid overdose which presented as classical Cushing's syndrome. Changes typical of glucocorticoid overdose were also observed in both hematological and clinical chemistry parameters. Effects on red blood cell parameters and a characteristic leucopenia, resulting from lymphopenia, accompanied by neutrophilia were observed. Recovery from these effects was not observed at 31 days after completion of treatment, which was attributed to the continued release of drug from the 'depot' at the injection site resulting in lymphoid depletion and thymic/ adrenal atrophy in both the rat and the dog, and glycogenic vacuolation of the liver in dogs. Post-mortem findings were also characteristic of glucocorticoid overdose and included lymphoid and thymic depletion, adrenal atrophy in both rats and dogs and glycogen deposition in the livers of dogs.

Inhalation repeated-dose toxicity studies were conducted with fluticasone propionate in rats and dogs for periods up to 78 and 52 weeks, respectively. In the rat study, animals received inhalation exposure via the nose because respiration in this species occurs almost entirely via the nose. Adverse reversible events were seen in the thymus (decreased weights in males and females receiving 14 or 61 µg/kg/day), adrenal weights (decrease weights in only in females). Histopathological examinations revealed a slight increase in the incidence of focal aggregations of alveolar macrophages in the lungs, centrilobular hepatocyte vacuolation in males receiving 14 or 61 µg/kg/day fluticasone propionate, and dose-related thymic involution in both sexes of these groups, all of which regressed by the end of the recovery period. An increased incidence of sinus histiocytosis and reduced cortical lymphoid cellularity were observed in lymph nodes of animals receiving 14 or 61 µg/kg/day fluticasone propionate. In the spleen, reduced cellularity of the white pulp, particularly of the thymus-dependent zone, occurred in animals receiving 14 or 61 µg/kg/day fluticasone propionate and this persisted in a small

number of animals after the recovery period. There were no histological changes observed in the adrenal glands and there was no evidence of irritation to the respiratory tract. Collectively, the results of this study are consistent with administration of high doses of a glucocorticoid drug and the majority of the observed effects were reversible. Similar findings, which were consistent with administration of high doses of a glucocorticoid drug, were observed in another 78 week study in rats, in which animals were treated by snout-only inhalation. Additional findings in this study included a slight increase in pancreatic masses in males receiving the high dose, which was associated with a higher number of islet cell adenomata and hyperplasia, and an increase in adipose replacement of exocrine tissue. Histopathological examinations revealed an increased incidence of adrenal pheochromocytomata in males receiving 57 µg/kg/day fluticasone propionate.

The results of inhalation repeated-dose toxicity studies with fluticasone propionate in dogs were similar to those observed in rats and are consistent with administration of high doses of a glucocorticoid drug. When administered by inhalation to dogs at doses of 2.5, 5, or 10 mg, twice daily for 10 days, fluticasone propionate caused no significant effects on body weight. However, reduced adrenal function, as evidenced by suppressed cortisol levels was observed on Day 10. Histopathological examinations revealed thymic involution, evidence of adrenal cortical hypofunction and glycogenic vacuolation of the liver. Similar results were observed following inhalation of 1, 3 or 9 mg/day fluticasone propionate to dogs for 43 or 44 days. Additional findings in animals receiving 3 or 9 mg/day fluticasone propionate included hematological changes, consisting of decreased erythrocyte and lymphocyte counts with increased neutrophil count, and clinical chemistry changes, consisting of increased alanine aminotransferase, alkaline phosphatase, total protein and albumin with decreased creatinine, all of which are associated with excessive steroid administration. Animals receiving 3 or 9 mg/day fluticasone propionate also exhibited increased liver weights, while all treated animals exhibited decreased thymus and adrenal weights. Relative spleen weights were significantly reduced in high dose treated females.

Histological changes included bone marrow hypoplasia, lymphoid depletion, adrenal cortex atrophy and hepatocyte vacuolation which were consistent with excessive steroid administration.

The long-term repeated-dose inhalation toxicity of fluticasone propionate was evaluated in a 26 week study in which dogs were administered 68, 170, or 510µg/day; a subset of dogs in each group were kept for an 8 week recovery period.. The results of this study were similar to those observed in the shorter duration inhalation studies in dogs, with marked reductions in plasma cortisol levels occurring in animals of the intermediate and high dose groups during the treatment period followed by a return to normal levels at 3 weeks after termination of treatment. Several hematological changes were observed in animals of the intermediate and high dose groups, including decreased leukocyte, lymphocyte and eosinophil counts and increased platelet count, all of which normalized by the end of the recovery period. Blood chemistry changes observed in animals of the intermediate and high dose groups included reduce plasma levels of glucose, urea, creatinine and aspartate aminotransferase with increased plasma level of total protein, alkaline phosphatase, potassium and cholesterol. All of these changes also regressed by the end of the recovery period. Post-mortem evaluations revealed decreased adrenal and uterus weight in animals receiving 170 and 510µg/day fluticasone propionate, with decreased thymus weights and increased liver weights in animals receiving 510µg/day offluticasone propionate. Findings from histopathological examinations were consistent with steroid administration and included thymic involution, lymphoid depletion of the lymph nodes, lymphoid atrophy within the spleen, atrophy of the adrenal zona fasciculata, bone marrow suppression, cytoplasmic rarefaction and/or cell swelling in the liver. All of these changes were dose related in incidence and severity and all had regressed by the end of the recovery period. Additional inhalation repeated-dose toxicity studies in dogs with treatment durations of 26 and 52 weeks revealed similar findings.

Local Tolerance

Several nonclinical studies were conducted to evaluate the local tolerance of fluticasone propionate and these included evaluations of intranasal tolerance in monkeys, ocular irritation in rabbits and contact sensitization in guinea pigs.

Intranasal tolerance of fluticasone propionate formulated in the finished product matrix was evaluated in Cynomolgus monkeys at fluticasone propionate doses of 0.2, or 0.4 mg/kg/day using metered-dose aerosol packs for 28 or 29 days. All animals survived the treatment and no clinical signs or evidence of irritation was noted. Histopathological examinations revealed no changes to the respiratory tract.

The acute ocular irritancy of fluticasone propionate was evaluated in rabbits using a modified Draize test where 10 mg of micronized fluticasone propionate powder was introduced into the conjunctival sac of the right eye of each treated animal, after which ocular irritation was evaluated at 0.5, 1, 3, 6, 24 and 72 hours after application.

Fluticasone propionate caused very slight conjunctival irritation at one hour after application, but had completely regressed by 3 hours after application. There were no adverse effects on the iris or cornea. Under the conditions of this study, fluticasone propionate was considered to be non-irritating to the eye.

The ability of fluticasone propionate to induce contact sensitization was evaluated in Guinea pigs. Treatment sites were assessed for the development of erythema at approximately 24 and 48 hours after sensitization challenge and were found to be negative.

Reproductive and Developmental Toxicity

Fertility and reproductive performance studies were conducted for fluticasone propionate in rats and teratogenicity studies were conducted in mice, rats and rabbits.

No evidence of impairment of fertility was observed in rats at subcutaneous doses up to 50 µg/kg (less than the MRHTDD on a mg/m² basis). Prostate weight was significantly reduced.

Fertility and general reproductive performance were evaluated in **rats** following subcutaneous administration of fluticasone propionate to F0 generation males and females during the periods of gametogenesis, mating, gestation, parturition and lactation with a developmental evaluation of the untreated F1 and F2 generations.

Under the conditions of this study, fluticasone propionate did not affect fertility, mating performance or the progress of pregnancy. Viability of F1 offspring of high dose dams

was reduced during the first few days post-partum. In litters from intermediate (30 µg/kg/day) and high dose (100 µg/kg/day) dams, pup weights were initially lower than controls but were similar in weights to control pups weight by the end of the lactation period.

Although morphologically normal, skeletal ossification was retarded and pups were smaller in size in the F1 offsprings of intermediate and high dose treated animals. No effects were noted on the reproductive function of either F1 or F2 generations.

Fluticasone propionate was subcutaneously administered to pregnant **mice** at doses of 15, 45, or 50µg/kg/day during gestation days (GD) 6 through 15. A slight reduction in food consumption and a dose-related reduction in body weight gain were noted in this study. Fluticasone propionate had no effect on fetal resorption, the number of live fetuses, or mean fetal weight. However, cleft palate was observed in 26 of 204 fetuses of the high dose group, and in 1 of 140 offspring of the intermediate dose group.

Treatment with fluticasone propionate in this study also resulted in retarded cranial ossification, as well as additional cranial sutural bones in offspring of the high dose group.

Subcutaneous administration of 10, 30, or 100µg/kg/day fluticasone propionate to female **rats** on GD 6-15 resulted in dose-related decreases in maternal body weights with no apparent effect on the incidence of post-implantation loss, number of live fetuses, or on fetal sex ratio. A dose-related decrease in mean fetal weight from the intermediate and high dose groups was noted compared to controls. Offspring of the high dose group also exhibited a greater incidence of retarded ossification and a few cases of omphalocele.

Studies in **rabbits** demonstrated the sensitivity of rabbits to glucocorticoids.

Subcutaneous administration of 30, 100, or 300 µg/kg/day fluticasone propionate on GD 8-20 caused total litter loss, which may have been caused partly by the prolonged exposure to the drug due to the continued release of drug from the injection site. In contrast to the findings from this study, oral administration of 3, 30, or 300 µg/kg/day fluticasone propionate to female rabbits on GD 8- 20 resulted in no treatment-related maternal effects or fetal effects (no change in pre- and post-implantation deaths, fetal weights, number and nature of implants, or fetal abnormalities).

The potential peri- and post-natal toxicity of fluticasone propionate was evaluated following subcutaneous administration of 5, 15, or 50 µg/kg/day fluticasone propionate to female **rats** from GD 17- 22 days after birth.

Development of the F1 generation was assessed by monitoring auditory and visual performance, locomotor coordination, curiosity, arousal, learning and memory.

Treatment with fluticasone propionate in this study resulted in reduced food consumption and body weight gain of treated dams from GD 17-21.

No significant effects were observed in the F1 generation. Treatment of the F0 generation with fluticasone propionate had no effects on the incidence of external fetal defects, fetal body weight, or sex ratio among the F2 generation.

Juvenile Toxicity Studies

Several nonclinical studies were conducted to evaluate the potential effects of fluticasone propionate on the development of juvenile animals. Subcutaneous administration of 1, 5 or 10 µg/kg/day fluticasone propionate to juvenile **rats** from day 8-43 of life did not affect survival or general health of treated rats. Male and female animals receiving 10µg/kg/day exhibited a reduced rate of body weight gain, but sexual maturation, as assessed by the descent of testes or vaginal opening, was unaffected. Examination of the epiphyses of the femur indicated no major corticosteroid effects on growth. A decrease in thymus weight was seen in animals receiving 5 or 10 µg/kg/day, but no corresponding histological changes were detected. Based on these findings, it was concluded that fluticasone propionate had no specific effects on the maturation of juvenile rats.

In a juvenile **dog** study, 5, 15 or 25 µg/kg/day fluticasone propionate was administered by head-only inhalation to 2-week-old dogs for 20 minutes per day for 7 weeks. There were no adverse developmental or irritation effects observed in the lungs or other respiratory tract structures among treated dogs. Treatment-related findings were limited to a decrease in body weight gain in male dogs of all groups and macroscopic and microscopic pathological changes in the adrenal glands, including atrophy of the zona fasciculata in the adrenals of males and females receiving 15 or 25 µg/kg/day.

In a separate juvenile dog study where fluticasone propionate was administered to juvenile dogs by face mask inhalation at doses of 7.2, or 52.6 µg/kg/day for 5 weeks, findings included a decrease in body weight gain, a marked decrease in plasma cortisol levels, atrophy of the zona fasciculata in the adrenal gland and depletion of lymphocytes in the thymus, which correlated with a decrease in adrenal and thymus weights in animals receiving 52.6µg/kg/day

Similar findings were observed in longer term studies with fluticasone propionate in **dogs**. In a 13 week study where juvenile dogs were administered fluticasone propionate by face mask inhalation at doses of 4, 12, or 29 µg/kg/day, no treatment related findings in clinical observations, ophthalmoscopic examinations, or in hematology/ clinical chemistry parameters were noted at any dose. There was no evidence of lung developmental impairment. The only effect noted was the slightly lower body weight gain for the high dose females when compared to the controls. Plasma cortisol levels were reduced in the intermediate and high dose groups in a dose related manner. Post-mortem evaluations revealed a reduction in adrenal weights in animals receiving the high dose, and histopathological examination revealed marked atrophy of the zona fasciculata in the adrenal glands of all animals receiving the high dose, with mild atrophy being observed in one intermediate animal. The adrenal findings are consistent with the exaggerated pharmacological responses to corticosteroids.

Endocrine Effects

Fluticasone propionate was screened for a wide range of steroid hormonal and antihormonal activity following subcutaneous administration to mice, rats and rabbits. The results of these studies demonstrated that fluticasone propionate did not have androgenic, estrogenic, anabolic or anti-gonadotrophic activities.

Genotoxicity

The genotoxic potential of fluticasone propionate was evaluated in both *in vitro* and *in vivo* test systems to examine its mutagenic and clastogenic potential. When evaluated in the *in vitro* microsome reverse mutation assay (Ames test), fluticasone propionate did not induce mutations (histidine revertants) to *Salmonella typhimurium* strains TA98,

TA100, TA1535 and TA1537 in either the presence or absence of metabolic activation at dose concentrations up to 500µg/plate.

Fluticasone propionate did not induce mutations (tryptophan revertants) to *Escherichia coli* strains B WP2 trpE, B WP2 trpE UvrA, or K-12 343/113 lys 60 at dose concentrations up to 100 µg/ml in both the presence and absence of metabolic activation. When tested *in vitro* for mitotic gene conversion at the his4 locus in *Saccharomyces cerevisiae*, fluticasone propionate did not induce mutations at dose concentrations up to 100µg/ml in both the presence and absence of metabolic activation.

Fluticasone propionate did not induce mutations in Chinese Hamster Ovary cells when tested in either the presence or absence of metabolic activation at dose concentrations up to 30µg/ml.

Fluticasone propionate was also tested *in vitro* for clastogenic potential in human peripheral lymphocytes at dose concentrations of 0.3, 1.0, 3.0, or 10.0 µg/ml in the presence or absence of metabolic activation. The results of this assay revealed no clastogenic activity for fluticasone propionate following exposure up to 24 hours.

Fluticasone propionate was evaluated in the *in vivo* micronucleus test where mice were administered either a single oral dose of 100, 300, or 1000 mg/kg, or as a single subcutaneous dose of 30, 100, or 300 mg/kg. Under the conditions of this study, administration of fluticasone propionate did not increase the frequency of micronucleated polychromatic erythrocytes in bone marrow cells.

Carcinogenicity Studies

The carcinogenic potential of fluticasone propionate was investigated in the mouse and rat following oral, dermal and inhalation administration. The results of these studies revealed no treatment-related effects on survival and no effects on the incidence or type

of neoplasm at any dose level administered. When orally administered to mice at doses of up to 1 mg/kg/day for 18 months, the systemic exposure to fluticasone propionate caused effects associated with excessive glucocorticoid exposure. However, no treatment-related effects on tumor type or incidence were detected.

Dermal administration with 40 µL of an ointment containing (b) (4) % fluticasone propionate to mice for 1, 3 or 7 days weekly for 80 weeks revealed no treatment-related effects on mortality or on the incidence of any tumor type.

Fluticasone propionate was also administered to rats by inhalation exposure in a study in which animals received daily 1 hour snout-only exposures to airstream concentrations of up to 2 µg/L fluticasone propionate from metered dose inhalers for 104 weeks.

Although systemic exposure to fluticasone propionate in this study was sufficient to cause hair loss and a dose-related reduction in body weight gain, there was no evidence of a treatment-related effect on mortality or an increased incidence of tumors.

Comments on Novel Excipients

No novel excipients were identified in this formulation. The sponsor is using the same formulation that was used in the approved prescription product. The inactive ingredients contained in Fluticasone Propionate (b) (4) Nasal Spray include: (b) (4) dextrose, (b) (4) (microcrystalline cellulose and carboxymethylcellulose sodium), phenylethyl alcohol, benzalkonium chloride, polysorbate 80 and purified water. All of these ingredients are of an approved pharmaceutical grade (Ph Eur, USP, NF) and comply with an internal standard.

Comments on Impurities and Degradants of Concern

The concentrations of the related impurity designated as (b) (4) (b) (4) as well as other individual identified impurities comply with the ICH qualification threshold of 1.0% or 50µg/day total daily intake.

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Integrated Overview and Conclusions

Fluticasone Propionate (b) (4) % Nasal Spray is an aqueous suspension of (b) (4) fluticasone propionate that is intended for topical administration to the nasal mucosa by means of a metering atomizing spray pump. Each 100 mg actuation delivered by the nasal spray adaptor contains 50 µg of fluticasone propionate which is a potent topical anti-inflammatory corticosteroid with low systemic activity. Fluticasone propionate is a glucocorticoid steroid with high topical anti-inflammatory potency, but with low systemic hypothalamic-pituitary-adrenal (HPA) suppressive activity following intranasal, inhalation or oral administration. The compound has no unexpected hormonal effects and no marked effects on the cardiovascular, respiratory or gastrointestinal systems, or on the central or peripheral autonomic nervous system.

Pharmacokinetic studies in rats and dogs have demonstrated the rapid and extensive metabolic clearance of fluticasone propionate. The results of these studies have shown that oral bioavailability of the drug is very low due to its limited absorption from the gastrointestinal tract and from extensive first-pass metabolism. Distribution studies have shown that only small traces of orally administered fluticasone propionate reach the systemic circulation and that any systemically available compound is rapidly eliminated in the bile and excreted in the feces. Animal studies have also demonstrated that fluticasone propionate does not accumulate in any tissues.

There are no concerns with the results of the repeated-dose toxicity studies either on the systemic effects of fluticasone propionate or on the local effects of the respiratory tract, confirming the safety profile of the drug when administered at lower doses via the intranasal, inhalation or oral routes. The adverse effects that were identified in these

studies were consistent with administration of high doses of a glucocorticoid drug and the majority of the observed effects were reversible upon discontinuation of treatment.

The nonclinical reproductive and developmental toxicity studies with subcutaneously administered fluticasone propionate revealed effects on embryofetal development that would be expected exaggerated pharmacological effects following exposure to a potent steroid. In contrast, oral administration of fluticasone propionate failed to produce the same effects, which was attributed to its low bioavailability via the oral route.

Fluticasone Propionate has a pregnancy category C. The use of Fluticasone Propionate (b) (4) % Nasal Spray during pregnancy should be undertaken only after careful consideration.

The results of the genotoxicity and carcinogenicity studies demonstrate that fluticasone propionate has no genotoxic or carcinogenic potential. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 µg/kg (approximately 4 and 10 times the maximum recommended human therapeutic daily dose (MRHTDD) for adults and children, respectively, on a mg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 µg/kg (less than and approximately equivalent to the MRHD for adults and children, respectively, on a mg/m² basis) for 104 weeks.

The nonclinical studies did not show adverse local effects for fluticasone propionate after nasal or ocular exposure; results were also negative for the test on contact sensitization.

No new inactive ingredients were used in this formulation.

There are no concerns with the levels of impurities or solvents for the proposed formulation.

In conclusion, the extensive nonclinical studies that were conducted with fluticasone propionate for the prescription product support the safe clinical use of Fluticasone Propionate (b) (4) Nasal Spray in the OTC setting under the recommended therapeutic dosage regimen. Based on the nonclinical evidence presented herein and on the extensive clinical history of the prescription Fluticasone Propionate (b) (4) Nasal Spray product, there are no novel safety concerns from the nonclinical perspective under the recommended conditions of use.

Appendix/Attachments

None

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

/s/

WAFA HARROUK
06/18/2014

PAUL C BROWN
06/27/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA number: 205-434

Applicant: GlaxoSmithKline Consumer Healthcare (GSKCH)

Stamp date: This fully electronic document was submitted on September 23, 2013

Drug name: Flonase® Allergy Relief (fluticasone propionate nasal spray) for OTC allergy symptom relief

NDA type: 505 (b)(1)

Indication: GSKCH has submitted this NDA as an Over-The-Counter (OTC) treatment for the relief of the nasal and ocular symptoms associated with allergic rhinitis in adults 18 years and older. These indications are expressed within the proposed OTC labeling as "...temporarily relieves the symptoms of nasal congestion, runny nose, sneezing, itchy nose, itchy and watery eyes due to hay fever, other upper respiratory allergies, (b) (4) (b) (4) ,,"

Background: the sponsor met with the FDA on May 16, 2013 to discuss the proposed contents and format of the NDA for Flonase Allergy Relief.

Relevant INDs/NDAs:

GSKCH is referring to the following IND and NDA to support *Flonase Allergy Relief* as an OTC treatment for allergic rhinitis:

- IND 28,636: Fluticasone propionate Aqueous Nasal Spray (GSKCH)
- NDA 20-121 Flonase Nasal 50 mcg spray (GSKCH)

On **initial** overview of the NDA application, this 505 (b) (1) submission does not seem to have any outstanding pharmacology/toxicology issues.

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?			N/A
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?			N/A
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND	x		No new nonclinical studies were requested for this NDA. This is a 505(b)(1) where the

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A
NEW NDA/BLA**

	Content Parameter	Yes	No	Comment
	studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?			sponsor is referring to their original nonclinical data for Flonase under IND 109,805 and NDA 20-121
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A. The sponsor is using the same formulation which was approved under NDA 20-121
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

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

/s/

WAFA HARROUK
11/07/2013

PAUL C BROWN
11/07/2013