HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ASMANEX TWISTHALER safely and effectively. See full prescribing information for ASMANEX TWISTHALER.

ASMANEX® TWISTHALER® (mometasone furoate inhalation powder), for oral inhalation use
Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	02/2021
Warnings and Precautions (5.1, 5.2)	02/2021

----------INDICATIONS AND USAGE----------

ASMANEX TWISTHALER is a corticosteroid indicated for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (1)

Limitations of Use: ASMANEX TWISTHALER is not indicated for the relief of acute bronchospasm (1, 5.2) or in children less than 4 years of age (1, 8.4).

---------- DOSAGE AND ADMINISTRATION ----------

- For oral inhalation only. (2)
- Instruct patients to inhale rapidly and deeply and, after administration, rinse mouth with water and spit out contents without swallowing. (2)

Recommended Dosages for ASMANEX TWISTHALER Treatment

Previous Therapy	Recommended Starting Dose	Highest Recommended Daily Dose
Patients ≥12 years who received bronchodilators alone	220 mcg once daily in the evening*	440 mcg†
Patients ≥12 years who received inhaled corticosteroids	220 mcg once daily in the evening*	440 mcg†
Patients ≥12 years who received oral corticosteroids‡	440 mcg twice daily	880 mcg
Children 4-11 years of age§	110 mcg once daily in the evening*	110 mcg*

*,†,‡,§ Please refer to section 2.1 for full dosage recommendations and details.

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation powder:

- 220 mcg TWISTHALER: delivers 200 mcg mometasone furoate per actuation. (3)
- 110 mcg TWISTHALER: delivers 100 mcg mometasone furoate per actuation. (3)

----------CONTRAINDICATIONS----------

- Patients with status asthmaticus or other acute episodes of asthma where intensive measures are required. (4)
- Patients with a *known* hypersensitivity to milk proteins or any ingredients of ASMANEX TWISTHALER. (4)

---------- WARNINGS AND PRECAUTIONS----------

- *Candida albicans* infection of the mouth and pharynx. Monitor patients periodically for signs of adverse effects in the mouth and pharynx. After administration, advise patients to rinse mouth with water and spit out contents without swallowing. (5.1)
- Deterioration of asthma or acute episodes: ASMANEX TWISTHALER should not be used for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Hypersensitivity reactions including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of ASMANEX TWISTHALER. Discontinue ASMANEX TWISTHALER if such reactions occur. (5.3)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.4)
- Risk of impaired adrenal function when transferring from oral steroids to inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ASMANEX TWISTHALER. (5.5)
- Hypercorticism, suppression of hypothalamic-pituitary-adrenal (HPA) function, with very high dosages or at the regular dosage in susceptible individuals. If such changes occur discontinue ASMANEX TWISTHALER slowly. (5.6)
- Reduction in bone mineral density with long-term administration. Monitor patients with major risk factors for decreased bone mineral content. (5.7)
- Suppression of growth in children. Monitor growth routinely in pediatric patients receiving ASMANEX TWISTHALER. (5.8)
- Glaucoma and cataracts. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use ASMANEX TWISTHALER long term. (5.9)
- Paradoxical bronchospasm may occur with ASMANEX TWISTHALER. Treat bronchospasm immediately with a fast-acting inhaled bronchodilator and discontinue use of ASMANEX TWISTHALER. (5.10)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with ASMANEX TWISTHALER. (5.11)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥5%) are headache, allergic rhinitis, pharyngitis, upper respiratory tract infection, sinusitis, oral candidiasis, dysmenorrhea, musculoskeletal pain, back pain, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Organon LLC, a subsidiary of Organon & Co., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ASMANEX® TWISTHALER® is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 4 years of age and older.

Limitations of Use

ASMANEX TWISTHALER is not indicated for the relief of acute bronchospasm.
ASMANEX TWISTHALER is not indicated in children less than 4 years of age.

2 DOSAGE AND ADMINISTRATION

Administration Information

Administer ASMANEX TWISTHALER by the orally inhaled route only. Instruct patients to inhale rapidly and deeply. After administration, advise patients to rinse the mouth with water and spit out contents without swallowing. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after initiation of treatment. After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients ≥12 years of age who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of ASMANEX TWISTHALER when administered in excess of recommended doses have not been established.

2.1 Recommended Dosages in Adult and Pediatric Patients 4 Years of Age and Older

The recommended starting doses and highest recommended daily dose for ASMANEX TWISTHALER treatment based on prior asthma therapy are provided in **Table 1**.

Table 1: Recommended Dosages for ASMANEX TWISTHALER Treatment

Previous Therapy	Recommended Starting Dose	Highest Recommended Daily Dose
Patients ≥12 years who received bronchodilators alone	220 mcg once daily in the evening*	440 mcg†
Patients ≥12 years who received inhaled corticosteroids	220 mcg once daily in the evening*	440 mcg†
Patients ≥12 years who received oral corticosteroids‡	440 mcg twice daily	880 mcg
Children 4-11 years of age§	110 mcg once daily in the evening*	110 mcg*

* When administered once daily, ASMANEX TWISTHALER should be taken only in the evening.

† The 440 mcg daily dose may be administered in divided doses of 220 mcg twice daily or as 440 mcg once daily.

‡ **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of ASMANEX TWISTHALER therapy. Monitor patients carefully for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency during steroid taper and

following discontinuation of oral corticosteroid therapy *[see Warnings and Precautions (5.5)]*.
§ Recommended pediatric dosage is 110 mcg once daily in the evening regardless of prior therapy.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder:

- ASMANEX TWISTHALER 220 mcg delivers 200 mcg mometasone furoate per actuation from the mouthpiece.
- ASMANEX TWISTHALER 110 mcg delivers 100 mcg mometasone furoate per actuation from the mouthpiece.

4 CONTRAINDICATIONS

ASMANEX TWISTHALER is contraindicated:

- Status Asthmaticus: in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

- Hypersensitivity: in patients with *known* hypersensitivity to milk proteins or any ingredients of ASMANEX TWISTHALER *[see Warnings and Precautions (5.3) and Description (11)].*

5 WARNINGS AND PRECAUTIONS

5.1 Oropharyngeal Candidiasis

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* occurred in 195 of 3007 patients treated with ASMANEX TWISTHALER. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while remaining on treatment with ASMANEX TWISTHALER therapy, but at times therapy with the ASMANEX TWISTHALER may need to be interrupted. After administration, advise patients to rinse the mouth with water and spit out contents without swallowing.

5.2 Acute Asthma Episodes

ASMANEX TWISTHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma. A short acting $beta_2$-agonist, such as albuterol, should be available at all times to treat acute asthma symptoms. Instruct patients to contact their physician immediately if episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with ASMANEX TWISTHALER. During such episodes, patients may require therapy with oral corticosteroids.

5.3 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions including rash, pruritus, angioedema, and anaphylactic reaction have been reported with use of ASMANEX TWISTHALER. Discontinue ASMANEX TWISTHALER if such reactions occur *[see Contraindications (4) and Adverse Reactions (6.2)].*

ASMANEX TWISTHALER contains small amounts of lactose, which contains trace levels of milk proteins. In postmarketing experience with ASMANEX TWISTHALER, anaphylactic reactions in patients with milk protein allergy have been reported *[see Contraindications (4) and Adverse Reactions (6.2)].*

5.4 Immunosuppression and Risk of Infections

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with

pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.5 Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who are transferred from systemically active corticosteroids to ASMANEX TWISTHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ASMANEX TWISTHALER may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ASMANEX TWISTHALER. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during treatment with ASMANEX TWISTHALER *[see Dosage and Administration (2.1)]*. Lung function (FEV_1 or PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to ASMANEX TWISTHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

5.6 Hypercorticism and Adrenal Suppression

ASMANEX TWISTHALER will often help control asthma symptoms with less suppression of HPA function than therapeutically similar oral doses of prednisone. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ASMANEX

TWISTHALER. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly when ASMANEX TWISTHALER is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ASMANEX TWISTHALER should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone furoate. The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

In a 2-year double-blind study in 103 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (baseline FEV_1 85%-88% predicted), treatment with ASMANEX TWISTHALER 220 mcg twice daily resulted in significant reductions in lumbar spine (LS) BMD at the end of the treatment period compared to placebo. The mean change from baseline to endpoint in the lumbar spine BMD was -0.015 (-1.43%) for the ASMANEX TWISTHALER group compared to 0.002 (0.25%) for the placebo group. In another 2-year double-blind study in 87 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (baseline FEV_1 82%-83% predicted), treatment with ASMANEX TWISTHALER 440 mcg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from baseline to endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the ASMANEX TWISTHALER group compared to -0.006 (-0.43%) for the placebo group.

5.8 Effect on Growth

Orally inhaled corticosteroids, including ASMANEX TWISTHALER, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ASMANEX TWISTHALER routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ASMANEX TWISTHALER, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Use in Specific Populations (8.4)]*.

5.9 Glaucoma and Cataracts

In clinical trials, glaucoma, increased intraocular pressure, and cataracts have been reported in 8 of 3007 patients following the administration of ASMANEX TWISTHALER. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use ASMANEX TWISTHALER long term.

5.10 Paradoxical Bronchospasm

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with ASMANEX TWISTHALER, it should be treated immediately with a fast-acting inhaled bronchodilator.
Treatment with ASMANEX TWISTHALER should be discontinued and alternative therapy instituted.

5.11 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ASMANEX TWISTHALER with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone furoate may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Oropharyngeal Candidiasis *[see Warnings and Precautions (5.1)]*
- Immunosuppression and Risk of Infections *[see Warnings and Precautions (5.4)]*
- Hypercorticism and Adrenal Suppression *[see Warnings and Precautions (5.6)]*
- Reduction in Bone Mineral Density *[see Warnings and Precautions (5.7)]*
- Growth Effects *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.4)]*
- Glaucoma and Cataracts *[see Warnings and Precautions (5.9)]*

6.1 Clinical Studies Experience

The safety data described below reflect exposure to ASMANEX TWISTHALER in 2380 patients with asthma exposed for 8 to 12 weeks and 627 patients with asthma exposed for 1 year in a total of 17 clinical trials.

In adult and adolescent patients 12 years of age and older, ASMANEX TWISTHALER was studied in 10 placebo-controlled clinical trials of 8 to 12 weeks duration with a total of 1750 patients receiving ASMANEX TWISTHALER. There were also 3 trials with a total of 475 patients receiving ASMANEX TWISTHALER for 1 year. In the 8- to 12-week clinical trials, the population was 12 to 83 years of age; 38% males and 62% females; and 83% Caucasian, 8% black, 6% Hispanic, and 3% other race/ethnicity. Patients received ASMANEX TWISTHALER 110 mcg twice daily (n=133), 220 mcg once daily in the morning (n=209), 220 mcg once daily in the evening (n=232), 220 mcg twice daily (n=433), 440 mcg once daily in the morning (n=419), 440 mcg once daily in the evening (n=250), or 440 mcg twice daily (n=74). In 3 long-term safety trials (two 9-month extensions of efficacy trials and one 52-week active-controlled safety trial), 475 patients with asthma (12-83 years of age, 44% males, 56% females, 87% Caucasian, 8% black, 4% Hispanic, and 1% other race/ethnicity) received various doses of ASMANEX TWISTHALER for 1 year.

In pediatric patients 4 to 11 years of age, ASMANEX TWISTHALER was studied in 3 placebo-controlled clinical trials of 12 weeks duration with a total of 630 patients receiving ASMANEX TWISTHALER and a 52-week, active-controlled safety trial with a total of 152 patients receiving ASMANEX TWISTHALER. In the 12-week clinical trials, the population was 4 to 11 years of age; 63% males and 37% females; and 67% Caucasian, 13% black, 17% Hispanic, and 3% other race/ethnicity. Patients received ASMANEX TWISTHALER 110 mcg once daily in the evening (n=98), 110 mcg once daily in the morning (n=181), 110 mcg twice daily (n=179), or 220 mcg once daily in the morning (n=172). In the long-term active-controlled safety trial (n=152), patients with asthma (4 to 11 years of age, 60% males and 40% females, 84% Caucasian, 11% Black, and 5% Hispanic) received ASMANEX TWISTHALER 110 mcg twice daily or 220 mcg once daily in the morning for 52 weeks.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 Years of Age and Older: The safety results of the 10 trials that were 8 to 12 weeks in duration were pooled because patients with asthma in these studies were previously maintained on bronchodilators and/or inhaled corticosteroids. The safety results of the one 12-week clinical trial in patients with asthma previously treated with oral corticosteroids are presented separately.

In the pooled 8- to 12-week clinical trials, adverse reactions were reported in 70% of patients treated with ASMANEX TWISTHALER (n=1750) compared to 65% of patients taking placebo (n=720). Table 2 displays the common adverse reactions (≥3% in any patient group receiving ASMANEX TWISTHALER) that occurred more frequently in patients treated with ASMANEX TWISTHALER compared to patients treated with placebo.

Table 2: Adverse Reactions with ≥3% Incidence in 10 Controlled Clinical Trials with ASMANEX TWISTHALER in Patients 12 Years of Age and Older Previously on Bronchodilators and/or Inhaled Corticosteroids				
	(%) of Patients			
	ASMANEX TWISTHALER			
Adverse Reaction	**220 mcg twice daily (n=433)**	**440 mcg once daily (n=497)**	**220 mcg once daily in the evening (n=232)**	**Placebo (n=720)**
Headache	22	17	20	20
Allergic Rhinitis	15	11	14	13
Pharyngitis	11	8	13	7
Upper Respiratory Infection	10	8	15	7
Sinusitis	6	6	5	5
Candidiasis, oral	6	4	4	2
Dysmenorrhea*	9	4	4	4
Musculoskeletal Pain	8	4	4	5
Back Pain	6	3	3	4
Dyspepsia	5	3	3	3
Myalgia	3	2	3	2
Abdominal Pain	3	2	3	2
Nausea	3	1	3	2
Average Duration of Exposure (Days)	81	70	80	62

* Percentages are based on the number of female patients.

The following other adverse reactions occurred in these clinical trials with an incidence of at least 1% but less than 3% and were more common on ASMANEX TWISTHALER therapy than on placebo:
Body as a Whole: fatigue, flu-like symptoms, pain
Gastrointestinal: gastroenteritis, vomiting, anorexia
Hearing, Vestibular: earache
Resistance Mechanism: infection
Respiratory: dysphonia, epistaxis, nasal irritation, respiratory disorder, throat dry

In the 12-week trial in adult asthmatics who previously required oral corticosteroids, the effects of ASMANEX TWISTHALER therapy administered as two 220-mcg inhalations twice daily (n=46) were compared with those of placebo (n=43). Adverse reactions, whether considered drug-related or not by the investigators, reported in more than 3 patients in the ASMANEX TWISTHALER treatment group, and which occurred more frequently than in placebo were (ASMANEX TWISTHALER % vs. placebo %): musculoskeletal pain (22% vs. 14%), oral candidiasis (22% vs. 9%), sinusitis (22% vs. 19%), allergic rhinitis (20% vs. 5%), upper respiratory infection (15% vs. 14%), arthralgia (13% vs. 7%), fatigue (13% vs. 2%), depression (11% vs. 0%), and sinus congestion (9% vs. 0%). In considering these data, an increased duration of exposure for patients on ASMANEX TWISTHALER treatment (77 days vs. 58 days on placebo) should be taken into account.

Long-Term Clinical Trials Experience - 12 Years of Age and Older: In 3 long-term safety trials, 475 patients with asthma 12 years of age and older were treated with ASMANEX TWISTHALER 220 mcg twice daily (n=60), 220 mcg once daily in the morning (n=41), 220 mcg once daily in the evening (n=40), 440 mcg once daily in the morning (n=44), 440 mcg once daily in the evening (n=41), 440 mcg twice daily (n=62), 880 mcg once daily (n=59), or at variable doses (n=128) for 52 weeks. The safety profile of ASMANEX TWISTHALER in the 52-week trials was similar to the findings in the 8- to 12-week clinical trials. In patients previously on inhaled corticosteroids, cataracts were reported in 3

patients (0.9%) treated with ASMANEX TWISTHALER, compared to 1 patient (1.7%) treated with the active comparator medication. Increased ocular pressure at the end of the study was observed in 2 patients, both on ASMANEX TWISTHALER 880 mcg once daily in the morning. Oral candidiasis, dysphonia, and dysmenorrhea were seen at a higher frequency with long-term administration than in the 8- to 12-week trials.

Pediatric Patients 4 to 11 Years of Age: In the three 12-week clinical trials in pediatric patients 4 to 11 years of age, patients with asthma were previously maintained on bronchodilators and/or inhaled corticosteroids. The safety results from 1 trial are described in Table 3 for ASMANEX TWISTHALER 110 mcg once daily in the evening. The safety results from the other 2 trials showed similar findings.

Overall adverse reactions were reported with approximately the same frequency by patients treated with ASMANEX TWISTHALER and those receiving placebo. Table 3 displays the common adverse reactions (≥2% in any patient group receiving ASMANEX TWISTHALER) that occurred more frequently in patients 4 to 11 years of age treated with ASMANEX TWISTHALER compared with placebo-treated patients.

Table 3: Adverse Reactions with ≥2% Incidence in a 12-Week Study with ASMANEX TWISTHALER in Patients 4 to 11 Years of Age Previously on Bronchodilators and/or Inhaled Corticosteroids

	(%) of Patients	
	ASMANEX TWISTHALER	
Adverse Reaction	**110 mcg once daily in the evening (n=98)**	**Placebo (n=99)**
Fever	7	5
Allergic Rhinitis	4	3
Abdominal Pain	6	2
Vomiting	3	2
Urinary Tract Infection	2	1
Bruise	2	0
Average Duration of Exposure (Days)	72	68

Long-Term Clinical Trials Experience in Children 4 to 11 Years of Age: In a 52-week, active-controlled, long-term safety trial, 152 patients with asthma 4 to 11 years of age were treated with ASMANEX TWISTHALER 110 mcg twice daily (n=74) or 220 mcg once daily (n=78). The safety profile for ASMANEX TWISTHALER in the 52-week trial was similar to the findings in the 12-week clinical trials.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of ASMANEX TWISTHALER. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: Vision blurred *[see Warnings and Precautions (5.9)]*.

Immune System Disorders: Immediate and delayed hypersensitivity reactions including rash, pruritus, angioedema and anaphylactic reaction *[see Warnings and Precautions (5.3) and Contraindications (4)]*.

Respiratory, Thoracic and Mediastinal Disorders: Asthma aggravation, which may include cough, dyspnea, wheezing and bronchospasm.

7 DRUG INTERACTIONS

In clinical studies, the concurrent administration of ASMANEX TWISTHALER and other drugs commonly used in the treatment of asthma was not associated with any unusual adverse reactions.

7.1 Inhibitors of Cytochrome P450 3A4

Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone furoate and potentially increase the risk for systemic corticosteroid side effects *[see Clinical Pharmacology (12.3)]*. Caution should be exercised when considering the coadministration of ASMANEX TWISTHALER with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin). Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ASMANEX TWISTHALER in pregnant women. There are clinical considerations with the use of ASMANEX TWISTHALER in pregnant women *[see Clinical Considerations]*. In animal reproduction studies with pregnant mice, rats, or rabbits, mometasone furoate caused increased fetal malformations and decreased fetal survival and growth following administration of doses that produced exposures approximately 1/3 to 8 times the maximum recommended human dose (MRHD) on a mcg/m^2 or AUC basis *[see Data]*. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

Animal Data

In an embryofetal development study with pregnant mice dosed throughout the period of organogenesis, mometasone furoate produced cleft palate at an exposure approximately 1/3 of the MRHD (on a mcg/m^2 basis with maternal subcutaneous doses of 60 mcg/kg and above) and decreased fetal survival at an exposure approximately equivalent to the MRHD (on a mcg/m^2 basis with a maternal subcutaneous dose of 180 mcg/kg). No toxicity was observed with a dose that produced an exposure approximately 1/10 of the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 20 mcg/kg and above).

In an embryofetal development study with pregnant rats dosed throughout the period of organogenesis, mometasone furoate produced fetal umbilical hernia at exposures approximately 6 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 600 mcg/kg and above) and delays in fetal ossification at exposures approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 300 mcg/kg and above).

In another reproductive toxicity study, pregnant rats were dosed with mometasone furoate throughout pregnancy or late in gestation. Treated animals had prolonged and difficult labor, fewer live births, lower birth weight, and reduced early pup survival at an exposure that was approximately 6 times the

MRHD (on an area under the curve (AUC) basis with a maternal subcutaneous dose of 15 mcg/kg). There were no findings with an exposure approximately 3 times the MRHD (on an AUC basis with a maternal subcutaneous dose of 7.5 mcg/kg).

Embryofetal development studies were conducted with pregnant rabbits dosed with mometasone furoate by either the topical dermal route or oral route throughout the period of organogenesis. In the study using the topical dermal route, mometasone furoate caused multiple malformations in fetuses (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at an exposure approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 150 mcg/kg and above). In the study using the oral route, mometasone furoate caused increased fetal resorptions and cleft palate and/or head malformations (hydrocephaly and domed head) at an exposure approximately 1/2 of the MRHD (on an AUC basis with a maternal oral dose of 700 mcg/kg). At an exposure approximately 2 times the MRHD (on an AUC basis with a maternal oral dose of 2800 mcg/kg), most litters were aborted or resorbed. No effects were observed at an exposure approximately 1/10 of the MRHD (on an AUC basis with a maternal oral dose of 140 mcg/kg).

8.2 Lactation

Risk Summary

There are no available data on the presence of ASMANEX TWISTHALER in human milk, the effects on the breastfed child, or the effects on milk production. Other inhaled corticosteroids, similar to mometasone furoate, are present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ASMANEX TWISTHALER and any potential adverse effects on the breastfed infant from ASMANEX TWISTHALER or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ASMANEX TWISTHALER for maintenance treatment of asthma as prophylactic therapy have been established in children 4 years of age and older. Use of ASMANEX TWISTHALER in pediatric patients 12 years of age and older is supported by evidence from adequate and well-controlled clinical trials in this patient population *[see Clinical Studies (14.1) and Adverse Reactions (6.1)]*.

Use of ASMANEX TWISTHALER in pediatric patients 4 to 11 years of age is supported by evidence from adequate and well-controlled clinical trials of 12 weeks duration in 630 patients 4 to 11 years of age receiving ASMANEX TWISTHALER and one 52-week safety trial in 152 patients *[see Clinical Studies (14.1) and Adverse Reactions (6.1)]*.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range: 0.3-1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents (4 years of age and older) receiving orally inhaled corticosteroids, including ASMANEX TWISTHALER, should be monitored routinely (e.g., via stadiometry).

A 52-week, placebo-controlled, parallel-group study was conducted to assess the potential growth effects of ASMANEX TWISTHALER in 187 prepubescent children (131 males and 56 females) 4 to 9 years of age with asthma who were previously maintained on an inhaled beta-agonist. Treatment groups included ASMANEX TWISTHALER 110 mcg twice daily (n=44), 220 mcg once daily in the morning (n=50), 110 mcg once daily in the morning (n=48), and placebo (n=45). For each patient, an average growth rate was determined using an individual regression approach. The mean growth rates, expressed as least-squares mean in cm per year, for ASMANEX TWISTHALER 110 mcg twice daily,

220 mcg once daily in the morning, 110 mcg once daily in the morning, and placebo were 5.34, 5.93, 6.15, and 6.44, respectively. The differences from placebo and the corresponding 2-sided 95% CI of growth rates for ASMANEX TWISTHALER 110 mcg twice daily, 220 mcg once daily in the morning, and 110 mcg once daily in the morning were -1.11 (95% CI: -2.34, 0.12), -0.51 (95% CI: -1.69, 0.67), and -0.30 (95% CI: -1.48, 0.89), respectively.

The potential growth effects of prolonged treatment with orally inhaled corticosteroids should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids, including ASMANEX TWISTHALER, each patient should be titrated to his/her lowest effective dose.

8.5 Geriatric Use

A total of 175 patients 65 years of age and over (23 of whom were 75 years of age and older) have been treated with ASMANEX TWISTHALER in controlled clinical trials. No overall differences in safety or effectiveness were observed between these and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

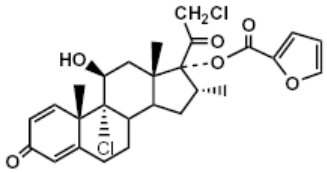
Concentrations of mometasone furoate appear to increase with severity of hepatic impairment *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.6)].* Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies, acute overdose is unlikely to require any treatment other than observation.

11 DESCRIPTION

Mometasone furoate, the active component of the ASMANEX TWISTHALER product, is a corticosteroid with the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) and the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight of 521.44 Daltons.

The ASMANEX TWISTHALER 110 mcg and 220 mcg products are cap-activated, inhalation-driven, multidose dry powder inhalers containing mometasone furoate and anhydrous lactose (which contains trace amounts of milk proteins).

Each actuation of the ASMANEX TWISTHALER 110 mcg or 220 mcg inhaler provides a measured dose of approximately 0.75 or 1.5 mg mometasone furoate inhalation powder, containing 110 or 220 mcg of mometasone furoate, respectively. This results in delivery of 100 or 200 mcg mometasone furoate from the mouthpiece, respectively, based on *in vitro* testing at flow rates of 30 L/min and 60 L/min with constant volume of 2 L. The amount of mometasone furoate emitted from the inhaler *in vitro* does not differ significantly for flow rates ranging from 28.3 L/min to 70 L/min at a constant volume of 2 L. However, the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow through the device. In adult and adolescent patients (aged ≥12 years) with varied asthma severity, mean peak inspiratory flow rate through the device was 69 L/min (range: 54-77 L/min). In pediatric patients (aged 5-12 years) diagnosed with asthma, mean peak inspiratory

flow rate in the 5- to 8-year-old subgroup was >50 L/min (minimum of 46 L/min) and for the 9- to 12-year-old subgroup was >60 L/min (minimum of 48 L/min).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory 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.

12.2 Pharmacodynamics

Adrenal Function: The effects of ASMANEX TWISTHALER on adrenal function have been evaluated in 2 clinical studies: 1 in adults 18 years of age and older and 1 in pediatric patients 6 to 11 years of age. Both clinical studies were specifically designed to assess the effect of ASMANEX TWISTHALER on adrenal function.

In a 29-day, randomized, double-blind, placebo-controlled study in 64 adult and adolescent patients 18 years of age and older with asthma, ASMANEX TWISTHALER 440 mcg twice daily and 880 mcg twice daily (twice the highest recommended daily dose) were compared to both placebo and prednisone 10 mg once daily as a positive control. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dL for the ASMANEX 440 mcg twice daily group (n=16) and 20.8 mcg/dL for the ASMANEX 880 mcg twice daily group (n=16), compared to 14.5 mcg/dL for the oral prednisone 10-mg group (n=16) and 25 mcg/dL for the placebo group (n=16). The difference between ASMANEX 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

In a 29-day, randomized, double-blind, placebo-controlled, parallel-group clinical trial in 50 pediatric patients 6 to 11 years of age with asthma, ASMANEX TWISTHALER 110 mcg twice daily, 220 mcg twice daily, and 440 mcg twice daily (2-8 times the highest pediatric daily recommended daily dose) were compared to placebo. HPA-axis function was assessed by 12-hour plasma cortisol AUC and 24-hour urinary-free cortisol concentrations. After 29 days of treatment, the mean changes in plasma cortisol $AUC_{0\text{-}12h}$ from baseline were -0.11, -19.5, -21.3, and -3.47 mcg•hr/dL for the treatment groups of ASMANEX TWISTHALER 110 mcg twice daily (n=12), 220 mcg twice daily (n=12), 440 mcg twice daily (n=11), and placebo (n=7), respectively. The mean differences from placebo in the groups treated with ASMANEX TWISTHALER 110 mcg twice daily, 220 mcg twice daily, and 440 mcg twice daily were 3.4 mcg•hr/dL (95% CI: -14.0, 20.7), -16.0 mcg•hr/dL (95% CI: -33.9, 1.9), and -17.9 mcg•hr/dL (95% CI: -35.8, 0.0), respectively. For 24-hour urinary-free cortisol, after 29 days of treatment, the mean changes from baseline were -1.53, -1.33, -6.70, and -4.68 mcg/day for the groups treated with ASMANEX TWISTHALER 110 mcg twice daily (n=12), 220 mcg twice daily (n=12), 440 mcg twice daily (n=12), and placebo (n=10), respectively. The mean differences in urinary-free cortisol changes from baseline compared to placebo were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6) for the groups treated with 110 mcg twice daily, 220 mcg twice daily, and 440 mcg twice daily, respectively.

12.3 Pharmacokinetics

Absorption: Following a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder to 6 healthy human subjects, plasma concentrations of unchanged mometasone furoate were shown to be very low compared to the total radioactivity in plasma. Following an inhaled single 400 mcg dose of ASMANEX TWISTHALER treatment to 24 healthy subjects, plasma concentrations for most subjects were near or below the lower limit of quantitation for the assay (50 pcg/mL). The mean absolute systemic bioavailability of the above single inhaled 400 mcg dose, compared to an intravenous 400 mcg dose of mometasone furoate, was determined to be less than 1%. Following administration of the recommended highest inhaled dose (400 mcg twice daily) to 64 patients for 28 days, concentration-time profiles were discernible, but with large intersubject variability. The coefficient of variation for C_{max} and AUC ranged from approximately 50% to 100%. The mean peak plasma concentrations at steady state ranged from approximately 94 to 114 pcg/mL and the mean time to peak levels ranged from approximately 1.0 to 2.5 hours.

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).

Elimination:

Metabolism: 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 CYP3A4 in the metabolism of this compound; however, no major metabolites were identified.

Excretion: 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.

Specific Populations:
Pharmacokinetics have not been adequately investigated with ASMANEX TWISTHALER by gender, race or in pediatric patients.

Patients with Hepatic Impairment: Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 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.

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

Drug Interaction Studies: *Inhibitors of Cytochrome P450 3A4:* In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211-324 pcg/mL).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 an 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 an mcg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies: In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on an mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the maximum recommended daily inhalation dose in adults on an mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on an mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an mcg/m^2 basis) produced delays in ossification but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an AUC basis).

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 an mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an area under the curve [AUC] basis). 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 (less than the maximum recommended daily inhalation dose in adults on an AUC basis).

14 CLINICAL STUDIES

14.1 Asthma

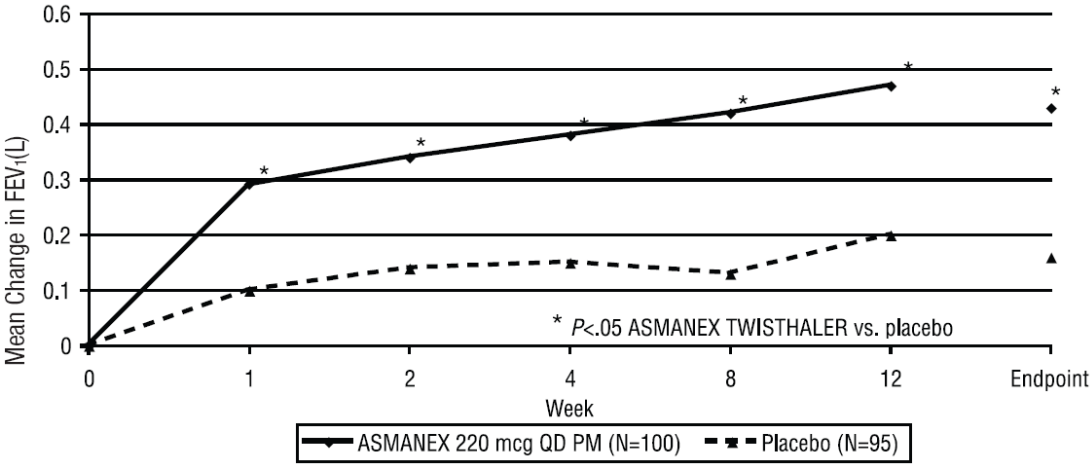
Adults and Adolescents 12 Years of Age and Older: The efficacy of ASMANEX TWISTHALER in patients with asthma 12 years and older was evaluated in ten 8- to 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trials. These trials included 1750 patients ranging from

12 to 83 years of age; 38% male and 62% female; and 83% Caucasian, 8% black, 6% Hispanic, and 3% other race/ethnicity. Patients received ASMANEX TWISTHALER 110 mcg twice daily (n=133), 220 mcg once daily in the morning (n=209), 220 mcg once daily in the evening (n=232), 220 mcg twice daily (n=433), 440 mcg once daily in the morning (n=419), 440 mcg once daily in the evening (n=250), or 440 mcg twice daily (n=74). The results of the clinical trials are presented based upon previous asthma therapy.

Patients ≥12 Years of Age Previously Maintained on Bronchodilators Alone: ASMANEX TWISTHALER was studied in three 12-week, double-blind trials in 737 patients with mild to moderate asthma (mean baseline $FEV_1 \cong 2.6$ L, 72% of predicted normal) who were maintained on short-acting $beta_2$-agonists alone. The first 2 trials evaluated doses of 440 mcg administered as 2 inhalations once daily in the morning and 1 of these studies also evaluated 220 mcg twice daily. In both trials, morning predose FEV_1 was significantly improved at endpoint (last observation) following treatment with 440 mcg ASMANEX TWISTHALER once daily in the morning as compared to placebo (14% vs. 2.5%, respectively, in 1 trial and 16% vs. 5.5% in the other). There was also a significant improvement in morning predose FEV_1 at endpoint following treatment with ASMANEX TWISTHALER 220 mcg twice daily. Other measures of lung function (morning and evening PEFR) also showed improvement compared to placebo. Patients receiving ASMANEX TWISTHALER treatment had reduced frequency of $beta_2$-agonist rescue medication use compared to those on placebo (mean reductions at endpoint 2.2 and 0.5 puffs per day, respectively, from a baseline of 4.1 puffs/day). Additionally, fewer patients receiving ASMANEX TWISTHALER 440 mcg once daily experienced asthma worsening than did patients receiving placebo.

In the third trial, 195 asthmatic patients were treated with ASMANEX TWISTHALER 220 mcg once daily in the evening or placebo. The morning FEV_1 at endpoint was significantly improved compared to placebo (mean change at endpoint 0.43 L or 16.8% vs. 0.16 L or 6%, respectively, see **Figure 1**). Evening PEF increased 24.96 L/min (7%) from baseline in the ASMANEX TWISTHALER group compared to 8.67 L/min (4%) in placebo.

FIGURE 1: A 12-Week Trial in Patients Previously Maintained on Inhaled $Beta_2$-agonists



Patients ≥12 Years of Age Previously Maintained on Inhaled Corticosteroids: The efficacy and safety of ASMANEX TWISTHALER in doses ranging from 110 mcg twice daily to 440 mcg twice daily was evaluated in 3 trials in 1072 patients previously maintained on inhaled corticosteroids. In the first 2 trials, asthmatic patients (mean baseline FEV_1 ~2.6 L, 76% predicted) were previously on either beclomethasone dipropionate [84-1200 mcg/day], flunisolide [100-2000 mcg/day], fluticasone propionate [110-880 mcg/day], or triamcinolone acetonide [300-2400 mcg/day]. The first trial included 307 patients who were treated in an open-label fashion with ASMANEX TWISTHALER 220 mcg (110 mcg x 2 inhalations) twice daily for 2 weeks followed by 12 weeks of double-blind treatment with ASMANEX TWISTHALER 440 mcg once daily in the morning or placebo. The second trial involved

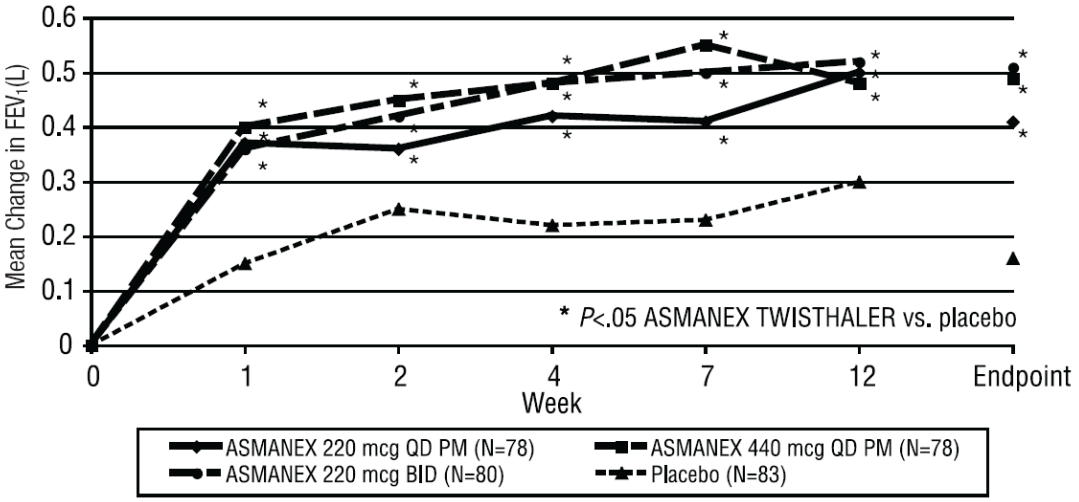
365 patients who continued on their previous dose of inhaled corticosteroids during a 2-week screening period before being switched to ASMANEX TWISTHALER 440 mcg twice daily, 220 mcg twice daily, 110 mcg twice daily, beclomethasone dipropionate 168 mcg twice daily, or placebo for 12 weeks.

In the first trial, morning predose FEV_1 was effectively maintained (-1.4% change from baseline to endpoint) over the 12 weeks in the patients who were randomized to ASMANEX TWISTHALER 440 mcg once daily in the morning, while decreasing 10% at endpoint in those switched to placebo. In addition, fewer patients treated with ASMANEX TWISTHALER experienced worsening of asthma compared to placebo.

In the second trial, morning predose FEV_1 was significantly increased at endpoint when patients were switched to ASMANEX TWISTHALER 220 mcg twice daily (7% increase) or 440 mcg twice daily (6.2% increase) as compared to a decrease of 7% when switched to placebo. Additionally, $beta_2$-agonist rescue medication use was decreased for patients who received ASMANEX TWISTHALER treatment relative to those on placebo (mean reduction from baseline to endpoint 1.1 puffs/day vs. increase of 0.7 puffs/day). Fewer patients receiving ASMANEX TWISTHALER treatment experienced asthma worsening than did patients receiving placebo.

The third trial evaluated the efficacy and safety of ASMANEX TWISTHALER compared to placebo in 400 asthmatic patients (mean FEV_1 67% predicted at baseline) previously maintained on beclomethasone dipropionate (hydrofluoroalkane [HFA] or chlorofluorocarbon [CFC]) 168-600 mcg/day, budesonide 200-1200 mcg/day, flunisolide 500-2000 mcg/day, fluticasone propionate 88-880 mcg/day, or triamcinolone acetonide 400-1600 mcg/day. Following a 28-day inhaled corticosteroid dose-reduction phase, patients were randomized to ASMANEX TWISTHALER 440 mcg once daily in the evening, 220 mcg once daily in the evening, 220 mcg twice daily, or placebo. At endpoint, patients who received ASMANEX TWISTHALER 220 mcg once daily in the evening, 440 mcg once daily in the evening, or 220 mcg twice daily had a significant improvement in morning FEV_1 [0.41 L (19%), 0.49 L (22%), and 0.51 L (24%) in the 220 mcg once daily in the evening, 440 mcg once daily in the evening, and 220 mcg twice daily treatment group, respectively] compared to placebo [0.16 L (8%)] (see Figure 2). Evening PEF increased 15.65 L/min (4.1%) with the 220 mcg once daily in the evening dose, 39.26 L/min (10.7%) with the 440 mcg once daily in the evening dose, and 36.7 L/min (10.8%) with the 220 mcg twice daily dose, respectively, compared to a 1.4 L/min (1%) increase with placebo. Patients receiving all doses of ASMANEX TWISTHALER treatment had reduced frequency of beta-agonist rescue medication use compared to those on placebo (mean reductions at endpoint of 1.4-1.8 puffs/day from a baseline of more than 3 puffs/day compared to an increase in use by 0.5 puffs/day for placebo). In addition, fewer patients receiving ASMANEX TWISTHALER experienced asthma worsening than did those on placebo.

FIGURE 2: A 12-Week Trial in Patients Previously Maintained on Inhaled Corticosteroids



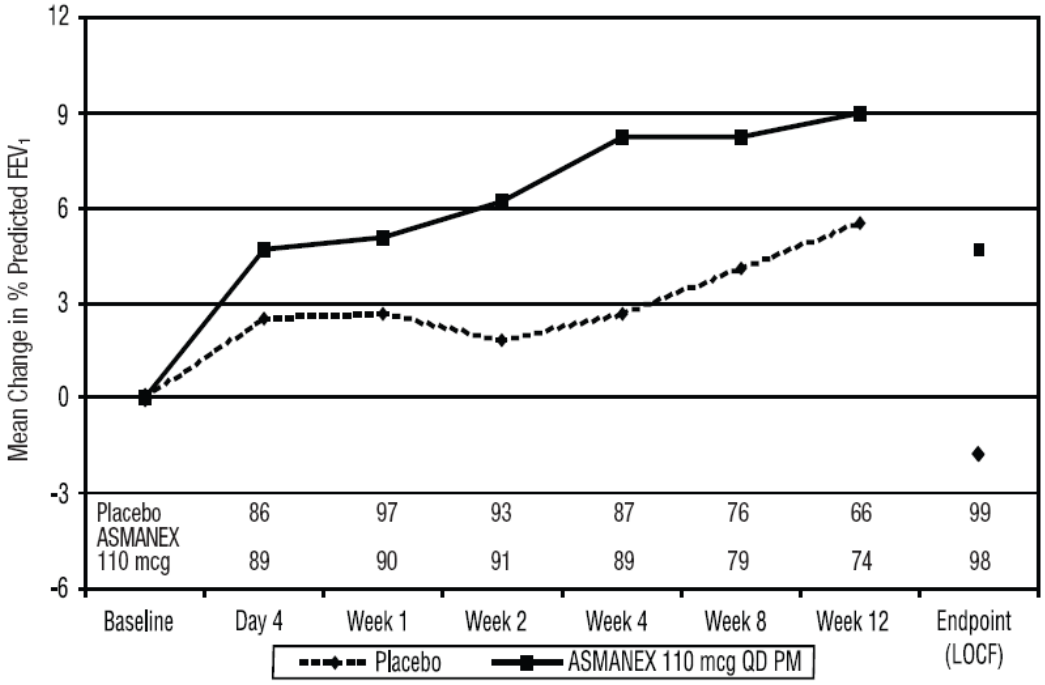
Patients ≥12 Years of Age Previously Maintained on Oral Corticosteroids: The efficacy of ASMANEX TWISTHALER 440 mcg and 880 mcg twice daily was evaluated in one 12-week, double-blind trial in patients previously maintained on oral corticosteroids. A total of 132 patients requiring oral prednisone (baseline mean daily oral prednisone requirement approximately 12 mg; baseline FEV_1 of 1.8 L, 59% of predicted normal), most of whom were also on inhaled corticosteroids (baseline inhaled steroid: beclomethasone dipropionate [168-840 mcg/day], budesonide [800-1600 mcg/day], flunisolide [1000-2000 mcg/day], fluticasone propionate [440-1760 mcg/day], or triamcinolone acetonide [400-2400 mcg/day]) were studied. Patients who received ASMANEX TWISTHALER 440 mcg twice daily had a significant reduction in their oral prednisone (46%) as compared to placebo (164% increase in oral prednisone dose). Additionally, 40% of patients on ASMANEX TWISTHALER 440 mcg twice daily were able to completely discontinue their use of prednisone, whereas 60% of patients on placebo had an increase in daily prednisone use. Patients on ASMANEX TWISTHALER had significant improvement in lung function (14% increase) compared to a 12% decrease in FEV_1 in the placebo group. Additionally, mean rescue $beta_2$-agonist use was reduced to approximately 3 puffs/day from a baseline of 4-5 puffs/day with ASMANEX TWISTHALER treatment, compared to an increase of 0.3 puffs/day on placebo. Patients who received ASMANEX TWISTHALER 880 mcg twice daily experienced no additional benefit beyond that seen with 440 mcg twice daily.

Pediatric Patients 4 to 11 Years of Age: The efficacy of ASMANEX TWISTHALER in patients with asthma 4 to 11 years of age was evaluated in three 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trials. These trials included 630 patients receiving ASMANEX TWISTHALER, ranging from 4 to 11 years of age; 63% male and 37% female; and 67% Caucasian, 13% black, 17% Hispanic, and 3% other race/ethnicity. Patients received ASMANEX TWISTHALER 110 mcg once daily in the evening (n=98), 110 mcg once daily in the morning (n=181), 110 mcg twice daily (n=179), or 220 mcg once daily in the morning (n=172). The results for 1 clinical trial are described below. The other 2 clinical trials support the efficacy of ASMANEX TWISTHALER.

A 12-week, placebo-controlled trial of 296 patients 4 to 11 years of age with asthma of at least 6 months duration (mean % predicted FEV_1 at baseline ranging from 77.3%-79.7%) was conducted to demonstrate the efficacy of the ASMANEX TWISTHALER in the treatment of asthma. Patients were treated with ASMANEX TWISTHALER 110 mcg once daily in the evening (n=98) or placebo (n=99) for 12 weeks. Assessment of efficacy was based upon morning predose FEV_1. The primary endpoint was the mean change from baseline to endpoint in percent-predicted FEV_1. For the primary endpoint, improvement in the ASMANEX TWISTHALER 110 mcg once daily in the evening treatment group (4.73) was statistically significant compared to placebo (-1.77). Figure 3 displays the results for % predicted FEV_1 change from baseline at endpoint.

In this study, secondary endpoints of morning and evening peak expiratory flow and rescue medication use were supportive of efficacy of ASMANEX TWISTHALER.

FIGURE 3: A 12-Week Trial in Children 4 to 11 Years of Age:
% Predicted FEV_1 Change from Baseline Over Time and at Endpoint by Treatment Group



Note: Endpoint=last available data for each subject

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ASMANEX TWISTHALER 220 mcg: delivers 200 mcg mometasone furoate from the mouthpiece

- comprised of an assembled plastic cap–activated dosing mechanism with dose counter, drug-product storage unit, drug-product formulation (135 mg for the 14 and 30 inhalation units and 240 mg for the 60 and 120 inhalation units), and mouthpiece, covered by a white screw cap that bears the product label.
- body of the inhaler is white and the turning grip is pink with a clear plastic window indicating the number of doses remaining. The inhaler will not deliver subsequent doses once the counter reaches zero (“00”).
- 14 inhalation units (Institutional Use Only; NDC# 78206-114-03)
- 30 inhalation units (NDC# 78206-114-04)
- 60 inhalation units (for more than 1 inhalation daily; NDC# 78206-114-02)
- 120 inhalation units (for more than 2 inhalations daily; NDC# 78206-114-01)

ASMANEX TWISTHALER 110 mcg: delivers 100 mcg mometasone furoate from the mouthpiece

- comprised of an assembled plastic cap–activated dosing mechanism with dose counter, drug-product storage unit, drug-product formulation (135 mg), and mouthpiece, covered by a white screw cap that bears the product label.
- body of the inhaler is white and the turning grip is gray with a clear plastic window indicating the number of doses remaining. The inhaler will not deliver subsequent doses once the counter reaches zero (“00”).
- 30 inhalation units (NDC# 78206-115-01)

Each inhaler is supplied in a protective foil pouch with Patient's Instructions for Use.

Storage and Handling
Store in a dry place at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Oropharyngeal Candidiasis
Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with ASMANEX TWISTHALER therapy, but at times therapy with ASMANEX TWISTHALER may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised *[see Warnings and Precautions (5.1)].*

Acute Asthma Episodes
Patients should be advised that ASMANEX TWISTHALER is not a bronchodilator and should not be used to treat status asthmaticus or to relieve acute asthma symptoms. Acute asthma symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol *[see Warnings and Precautions (5.2)].*

Hypersensitivity Reactions Including Anaphylaxis
Hypersensitivity reactions including rash, pruritus, angioedema and anaphylactic reaction have been reported with use of ASMANEX TWISTHALER. Discontinue ASMANEX TWISTHALER if such reactions occur *[see Contraindications (4), Warnings and Precautions (5.3), and Adverse Reactions (6.2)].*

ASMANEX TWISTHALER contains small amounts of lactose, which contains trace levels of milk proteins. In postmarketing experience with ASMANEX TWISTHALER, anaphylactic reactions in patients with milk protein allergy have been reported *[see Contraindications (4) and Adverse Reactions (6.2)].*

Immunosuppression and Risk of Infections
Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex *[see Warnings and Precautions (5.4)].*

Hypercorticism and Adrenal Suppression
Patients should be advised that ASMANEX TWISTHALER may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ASMANEX TWISTHALER *[see Warnings and Precautions (5.6)]*.

Reduction in Bone Mineral Density
Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition *[see Warnings and Precautions (5.7)].*

Reduced Growth Velocity

Patients should be informed that orally inhaled corticosteroids, including mometasone furoate inhalation powder, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route *[see Warnings and Precautions (5.8)].*

Use Daily for Best Effect

Patients should be advised to use ASMANEX TWISTHALER at regular intervals, since its effectiveness depends on regular use. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. If symptoms do not improve in that time frame or if the condition worsens, patients should be instructed to contact their physician.

Instructions for Use

Patients should be instructed to record the date of pouch opening on the cap label and discard the inhaler 45 days after opening the foil pouch or when the dose counter reads “00” and the final dose has been inhaled, whichever comes first. The inhaler should be held upright while removing the cap. The medication should be taken as directed, breathing rapidly and deeply, and patients should not breathe out through the inhaler. The mouthpiece should be wiped dry and the cap replaced immediately following each inhalation and rotated fully until the click is heard. After administration, the patient should rinse their mouth with water and spit out contents without swallowing. Patients should store the unit as instructed. The dose counter displays the doses remaining. When the dose counter indicates zero, the cap will lock and the unit must be discarded. Patients should be advised that if the dose counter is not working correctly, the unit should not be used and it should be brought to their physician or pharmacist.

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For patent information: www.organon.com/our-solutions/patent/

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