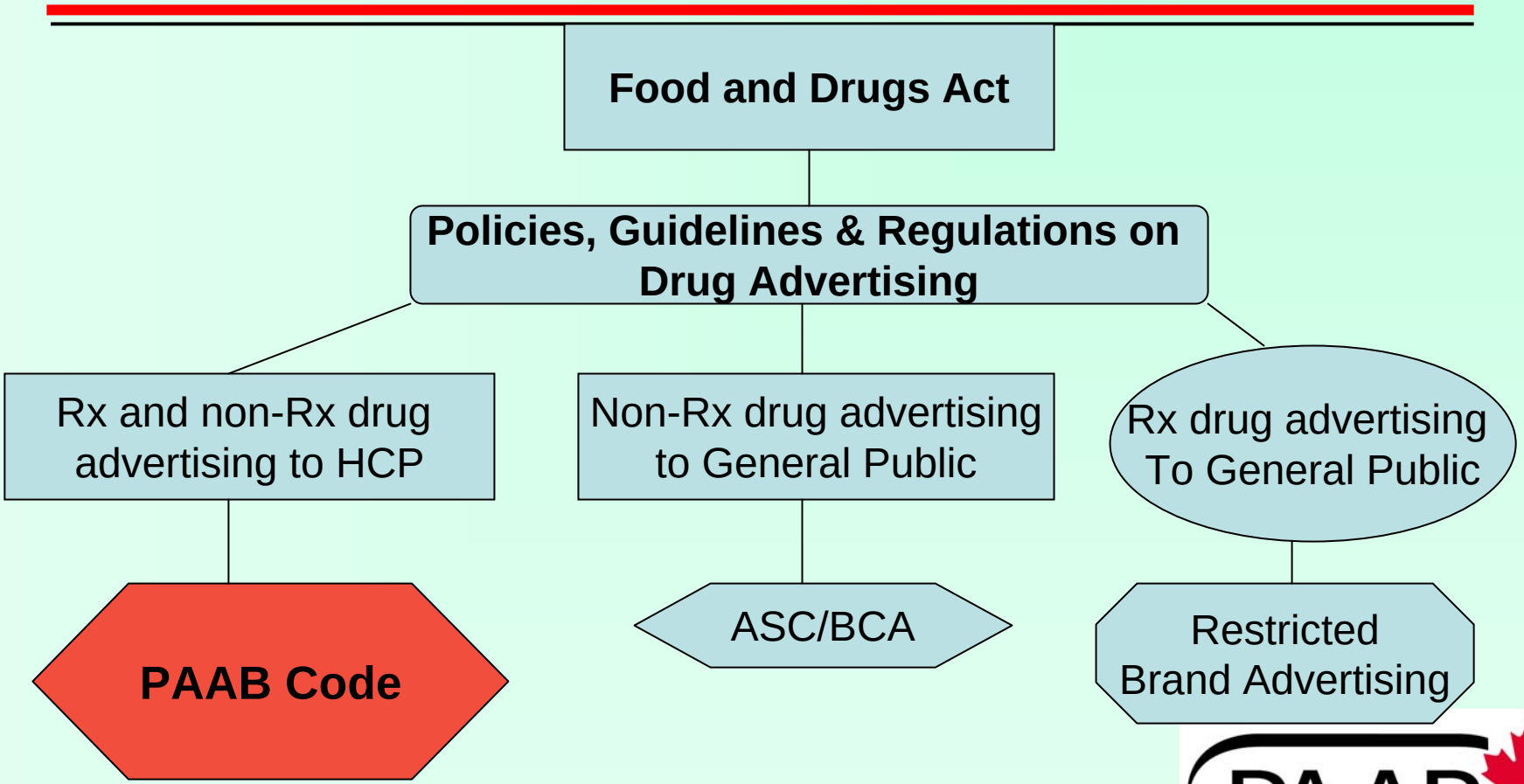
CAPRA

November 26, 2007

Ray Chepesiuk
PAAB Commissioner

- PAAB Facts
- PAAB Activities – 2007 -2008
- Code PI change
- e-Files
- How to get Approval Fast

Regulatory Overview of Healthcare Product Advertising in Canada

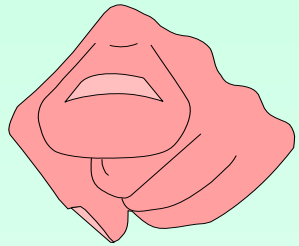


PAAB:
Serving the Two Headed monster

Self-regulation

means

YOU



Self-Regulation

- Goal is to benefit society
- Law is the minimum standard
- Direct participation by industry
- Helps maintain “level playing field”
- Flexible alternative to legislative regulation
- Cost-recovery, no tax dollars
- Continuous monitoring
- Collective wisdom

"20% of the regulated population will automatically comply with any regulation, 5% will attempt to evade it, and 75% will comply so long as they think the 5% will be caught and punished."

Chester Bowles - regulator and member in the 1941 U.S. Wartime Office of Price Administration

PAAB - (since 1976)

- **Independent, not-for-profit review agency**
- **Primary role: ensure advertising of prescription drugs is accurate, balanced and evidence-based**
- **Self-regulation: a pre-clearance review mechanism in co-operation with industry, HC professionals, media, consumers, government**

Product Scope of Code

The Code applies to all communications in which claims, quotations and references are made for healthcare products, meaning single entity and compound prescription and non-prescription pharmaceutical products, biologicals, and natural health products.

Target Audience Scope

The Code applies to all APS and institutional messages directed to licensed members of the professions of medicine, dentistry, naturopathy, nursing, pharmacy and related health disciplines and institutions.

Direct-to-Consumer Scope

The PAAB provides a user fee advisory service on direct to consumer promotional activities regarding the treatment of disease with Federal Drug Schedule F and Schedule D biological drugs that would require a prescription for sale in Canada

PAAB's Board of Directors

- Three pharmaceutical trade associations
- NDMAC, Rx&D, CGPA
- Health professionals - CMA, CPhA, FMSQ, AFMC
- Best Medicines Coalition (BMC)
- Canada's Assoc for the Fifty-Plus (CARP)
- Can Assoc of Medical Publishers (CAMP)
- Advertising industry (AMAA)
- Chair, Vice-chair, Treasurer

Health Canada Santé Canada

- **Health Canada is an ex-officio observer and advisor "without relinquishing authority under the Food and Drugs Act"**
- **PAAB Commissioner liaison with Manager, Advertising and Risk Communications Section, Marketed Health Products Directorate**
  - **"*PAAB and Therapeutic Products Directorate Roles and Consultation Related to Advertising Review*"**

PAAB

Food & Drugs Act and Regulations

"Advertising"

"any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device"

-section 2 of Food Drugs Act

PAAB Advertising Definition

- Any **paid** message communicated by Canadian media with the intent to influence the choice, opinion or behavior of those addressed by commercial messages
- direct or indirect promotion

Independence

- “freedom from the control, influence, support, aid, or the like, of others.”

- Dictionary.com

Policy
Direct Transfer to Health Canada

- **Complaints including safety allegations**
- **Complaints about Direct-to-Consumer prescription drug advertising**
- **Complaints about advertising of unapproved products**
- **Noncompliance with PAAB rulings applies to all companies**

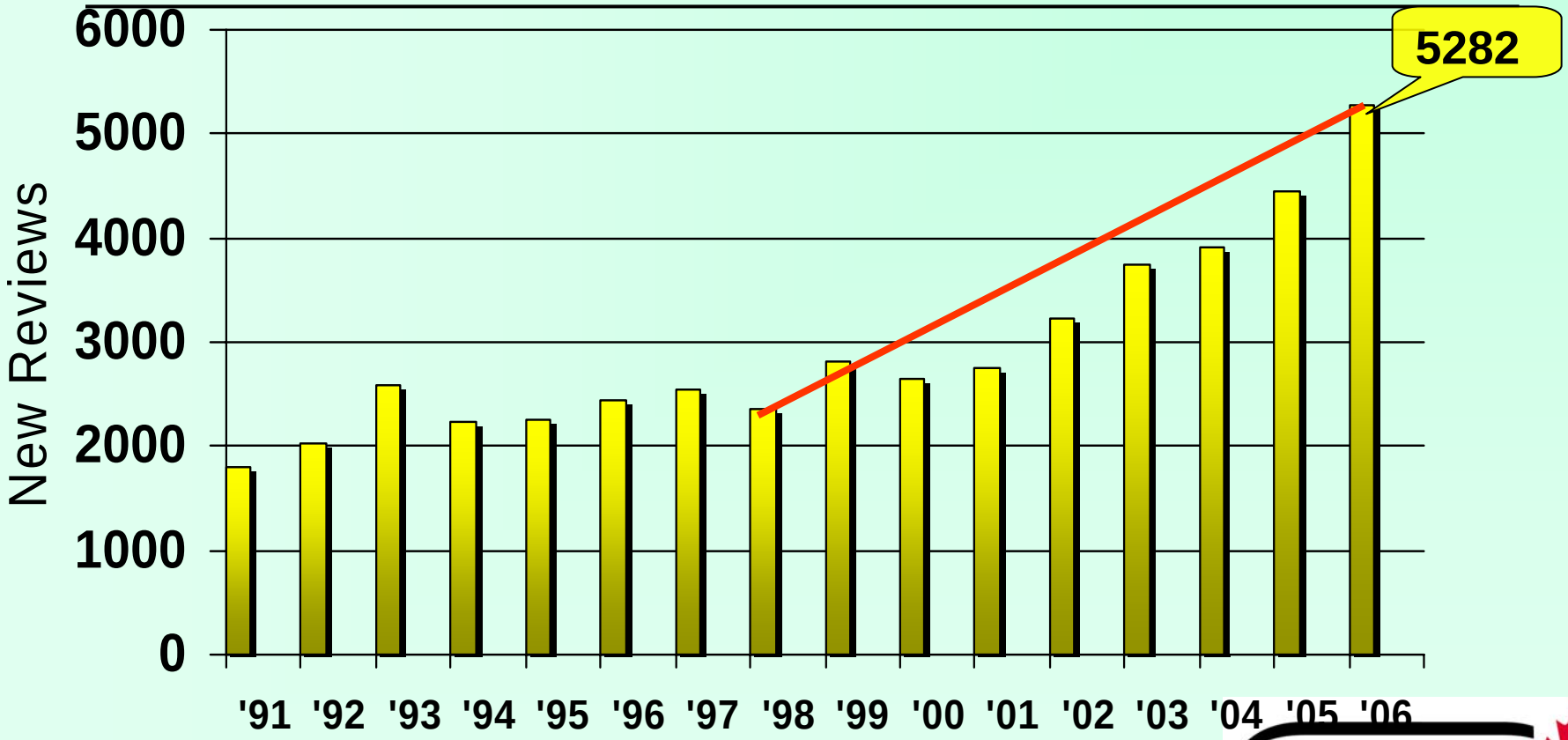
PAAB Review Staff

- **Reviewers - Colin Campbell, Yin Man, Lucia Kim, Pauline Dong, Patrick Massad, Chris Seto, Karen Rizwan, Ellen Fan**
- **Chief Review Officer - John Wong**
- **Admin Assistants – Estelle Parkin, Laurie Johns, Sabrina Hack**
- **Manager, Finance & Admin – Glenn Golaz**
- **Commissioner: Ray Chepesiuk**

PAAB Review Timelines

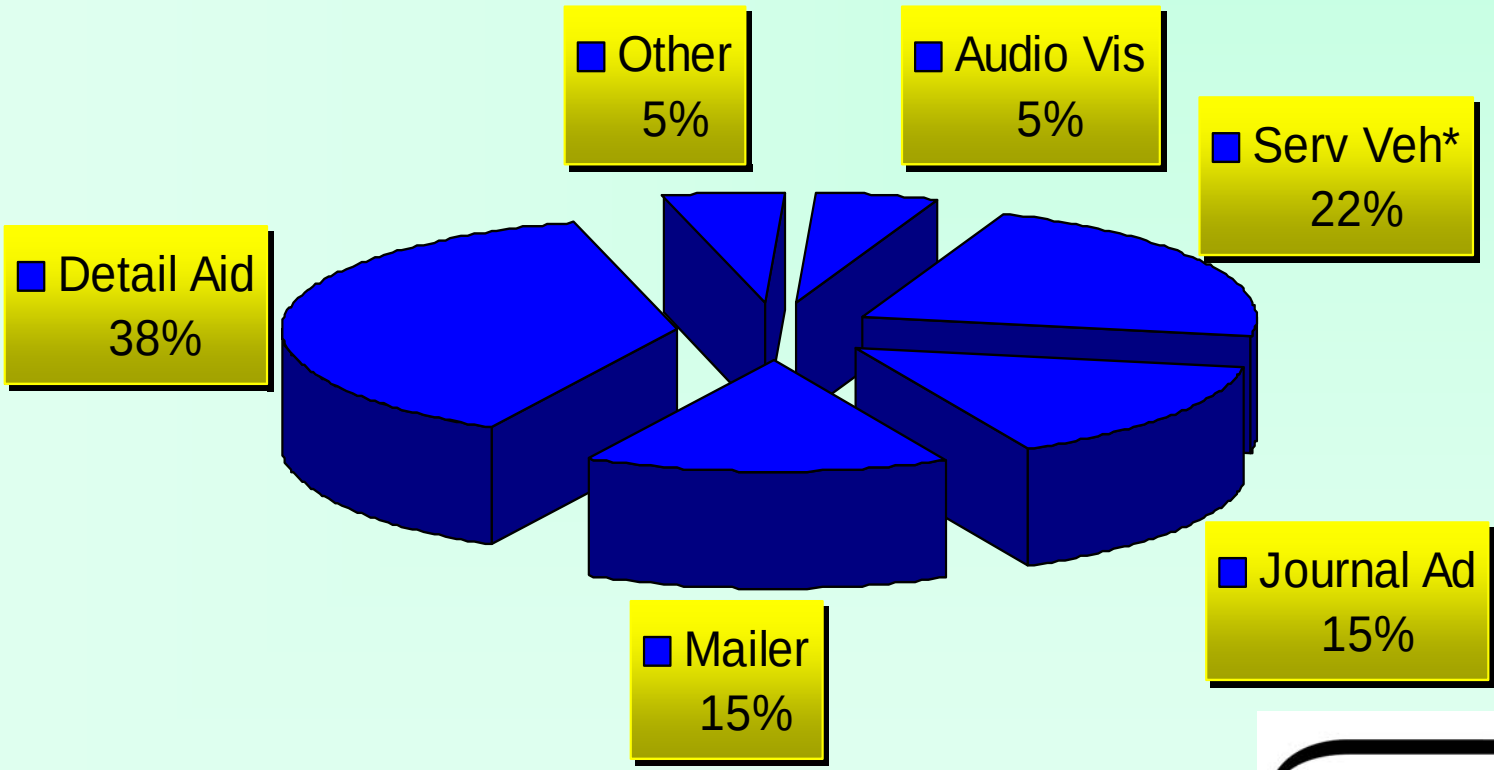
- **10-day Turn-around to first review (or less) – 100% in 2007**
- **Revisions picked up usually in 3 days**
- **Review volume ~ 5,000 new submissions annually and ~18,000 total review files with revisions and second language**

Number of Reviews



PAAB

Types of Advertising/Promotion System (APS) - 2006



(*)Service vehicle: Pt info, charts, counselling tools

PAAB

Review Performance

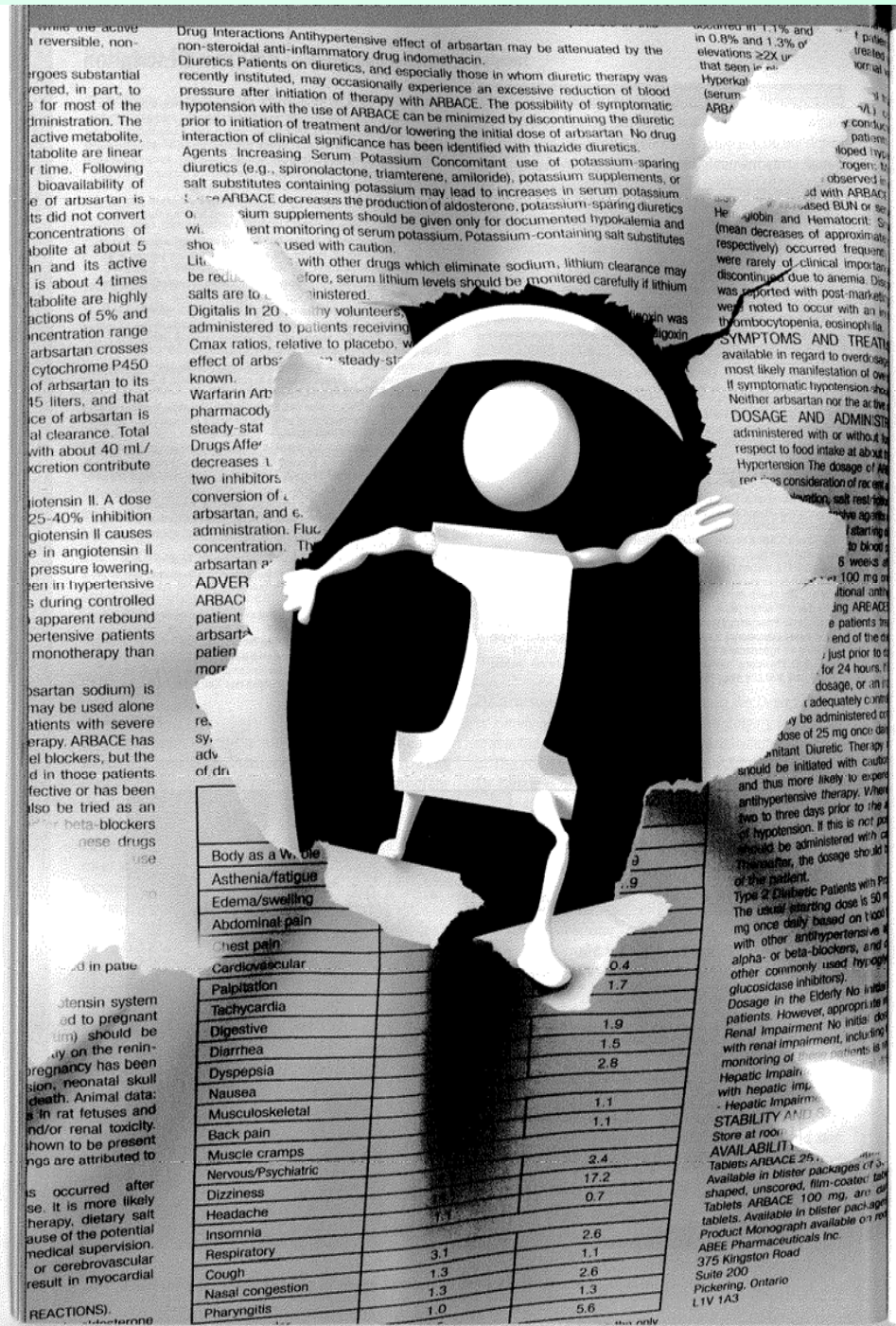
4,282 new files to October 31, 2007

Turnaround to first review

10 days – 5%	5 days – 15.2%
9 days - 8%	4 days – 13%
8 days – 7%	3 days – 12.4%
7 days – 9.8%	2 days – 9%
6 days – 13.4%	1 day or less – 6%

PAAB Activities - 2007

- Code Revision – July 1 – info days
- E-files – January 2, 2008
- Workshops in November
- 4-day turnaround time for DTCARx and Opinions – April 1, 2007
- New Board Members – Chair, Vice Chair, AFMC
- Strategic Plan
- Communications Plan
- Client Surveys/Focus Groups



Body as a W. ole		
Asthenia/fatigue		.9
Edema/swelling		
Abdominal pain		
Chest pain		
Cardiovascular		0.4
Palpitation		1.7
Tachycardia		
Digestive		1.9
Diarrhea		1.5
Dyspepsia		2.8
Nausea		
Musculoskeletal		1.1
Back pain		1.1
Muscle cramps		
Nervous/Psychiatric		2.4
Dizziness		17.2
Headache		0.7
Insomnia		
Respiratory		2.6
Cough	3.1	1.1
Nasal congestion	1.3	2.6
Pharyngitis	1.3	1.3
	1.0	5.6

Introducing an easier way to get the Product Information you need.

You asked. We delivered. The **Pharmaceutical Advertising Advisory Board (PAAB)** has changed the ***format*** of drug advertising to help you cut through the clutter of fine print. Not only have we reduced the amount of small type in ads, but we've added a tab to guide you directly to the corresponding Product Information. Once there, you'll notice that the Prescribing Summary has been categorized into the following convenient sections:

- Patient Selection Criteria
- Safety Information
- Administration
- Study References

Look for the i icon at the bottom of each ad to get to the information you need, faster.

PAAB

For over 30 years, the PAAB has been an independent, non-profit regulatory body which helps ensure that drug advertisements are accurate, balanced, and evidence-based.

Direct access to the drug information you need.

BRIEF PRESCRIBING INFORMATION

NAME OF DRUG

DIOVAN® (valsartan) Tablets, 40 mg, 80 mg, 160 mg and 320 mg
DIOVAN®-HCT (valsartan and hydrochlorothiazide)
Tablets, 80 mg/12.5 mg, 160 mg/12.5 mg, and 160 mg/25 mg

PHARMACOLOGICAL CLASSIFICATION

DIOVAN®: Angiotensin II AT1 Receptor Blocker
DIOVAN®-HCT: Angiotensin II AT1 Receptor Blocker and Diuretic

INDICATIONS AND CLINICAL USE

Hypertension

DIOVAN® and DIOVAN®-HCT are indicated for the treatment of mild to moderate essential hypertension.

DIOVAN® may be administered alone, or concomitantly with thiazide diuretics.

DIOVAN®-HCT is not indicated for initial therapy and is indicated when combination therapy is appropriate.

The safety and efficacy of concurrent treatment with DIOVAN® and angiotensin-converting enzyme inhibitors have not been established.

Following Myocardial Infarction

DIOVAN® is indicated to reduce cardiovascular mortality in clinically stable patients with signs or symptoms of left ventricular dysfunction in conjunction with acute myocardial infarction when the use of an angiotensin-converting enzyme inhibitor (ACEI) is not appropriate. The combination of DIOVAN® and an angiotensin-converting enzyme inhibitor (ACEI) has not been shown to result in clinically relevant improvement in cardiovascular outcome over DIOVAN® use alone; such combined use is not recommended.

CONTRAINDICATIONS

DIOVAN® and DIOVAN®-HCT are contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, DIOVAN®-HCT is also contraindicated in patients with anuria, and in patients hypersensitive to other sulfonamide-derived drugs.

WARNINGS

Serious Warnings

When used in pregnancy during the second and third trimesters, angiotensin II receptor (AT_1) Antagonist can cause injury to or even death of the developing fetus. When pregnancy is detected, DIOVAN® should be discontinued as soon as possible.

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, DIOVAN® and DIOVAN®-HCT should be discontinued as soon as possible. Drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy have been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development, prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, possibly due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure limited to the first trimester. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken DIOVAN®.

Mothers whose embryos and fetuses are exposed to an angiotensin II AT1 receptor blocker only during the first trimester should be so informed. Nonetheless, when patients become pregnant, use of DIOVAN® should be discontinued as soon as possible. Rarely (probably less than one in every thousand pregnancies), no alternative to angiotensin II AT1 receptor blocker will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations performed to assess intra-amniotic environment. If oligohydramnios is observed, DIOVAN® should be discontinued unless considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreparable injury. Infants with histories of *in utero* exposure to an angiotensin II AT1 receptor blocker should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed to support of blood pressure and renal perfusion. Exchange transfusion may be required to reverse hypotension and/or substitute for impaired renal function. DIOVAN® is not removed from plasma by dialysis. Thiazides cross the placental barrier and appear in cord blood. Routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia. *Animal Data:* No teratogenic effects were observed when DIOVAN® was administered orally to pregnant mice and rats at doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate and slight delays in developmental milestones were observed in studies in which parental rats were treated orally with DIOVAN® at maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of DIOVAN®, in some cases after the first dose. It is more likely to occur in patients volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, due to potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease; excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. Caution should be exercised when initiating therapy after acute myocardial infarction. Patients with heart failure, or in the early post-myocardial infarction period, who are given DIOVAN® commonly have some reduction in blood pressure, but discontinuation of therapy is usually not necessary if well screened prior to treatment and found to be clinically stable. If symptomatic hypotension occurs, consideration should be given to dosage reduction (see DOSAGE AND ADMINISTRATION, Following Myocardial Infarction). In patients treated following myocardial infarction, the recommended regimen of DIOVAN® has been observed to result in a greater incidence of hypotension as a serious adverse event than the conventional dosage regimen of captopril in this indication (see ADVERSE REACTIONS, Following Myocardial Infarction).

Azotemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Hypersensitivity Reactions

Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

PRECAUTIONS

Renal Impairment

With inhibition of the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. When renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as in patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Following myocardial infarction, major renal dysfunction was observed to occur more frequently with DIOVAN® than with captopril monotherapy. The role of modestly lower blood pressure that may occur with DIOVAN® compared to captopril monotherapy, is not known. The incidence of clinically relevant hyperkalemia has also been observed to be increased with DIOVAN® (see ADVERSE REACTIONS, Laboratory Findings). Patients exposed to potassium-sparing diuretics and/or potassium supplements were more likely to develop hyperkalemia; their use should be carefully monitored or avoided (see Drug Interactions, *Agents Increasing Serum Potassium*). Use of DIOVAN® should include appropriate assessment of renal function. Thiazides should be used with caution. Because of the hydrochlorothiazide component, DIOVAN®-HCT is not recommended in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

Patients with Impaired Liver Function

In general, no dosage adjustment is needed in patients with mild to moderate liver disease. However, care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of DIOVAN® is eliminated in the bile. No information is available in patients with severe liver disease.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolism

Patients receiving thiazides should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia). Periodic determinations of serum electrolytes to detect possible electrolyte disturbance should be performed at appropriate intervals. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability). Any chloride deficit during thiazide therapy is generally mild usually not requiring specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion when treated with vasodilators, because they do not develop as much afterload reduction.

Use in Nursing Mothers

It is not known whether DIOVAN® is excreted in human milk but it was excreted in the milk of lactating rats. Thiazides appear in human milk. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

The safety and effectiveness of DIOVAN® and DIOVAN®-HCT in children and adolescents (below the age of 18 years) have not been established and use in this age group is not recommended.

Use in the Elderly

Of the 2542 patients receiving DIOVAN® monotherapy in placebo-controlled clinical trials, 31% were 65 years and older. No overall age-related differences were seen in the adverse effect profile but due to potential for greater sensitivity in some older individuals, appropriate caution is recommended.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience excessive reduction in blood pressure after initiation of therapy with DIOVAN®. The possibility of symptomatic hypotension with the use of DIOVAN® can be minimized by discontinuing the diuretic prior to initiation of treatment (see WARNINGS, Hypotension and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium: Since DIOVAN® decreases production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium when DIOVAN® therapy is instituted. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect of DIOVAN® on serum potassium.

Lithium Salts: As with other drugs which eliminate sodium, lithium clearance may be decreased in the presence of DIOVAN®. Serum lithium levels should be monitored carefully if lithium salts are administered with DIOVAN®. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium adding a high risk of lithium toxicity.

Warfarin: Co-administration of DIOVAN® and warfarin over 5 days did not affect the bioavailability of DIOVAN®. Co-administration of DIOVAN® and warfarin resulted in a 12% increase in prothrombin time (PT) but had no effect on activated partial thromboplastin time (APTT).

Digoxin: A single dose of digoxin administered with a single dose of DIOVAN® did not result in a clinically significant interaction. No steady state data are available. Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.

d-Tubocurarine: Thiazide drugs may increase the responsiveness to tubocurarine.

Insulin: Insulin requirements in diabetic patients treated with diuretics may be increased, decreased or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Alcohol, Barbiturates, or Narcotics: Diuretic potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia, may occur when steroids are given concomitantly with diuretics.

Pressor Amines (e.g. norepinephrine): In the presence of diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude use.

Non-Steroidal Anti-Inflammatory Drugs: In some patients, administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. When DIOVAN®-HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Others: Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycemic effect of diazoxide, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects. The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden); apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa. Absorption of thiazide diuretics is decreased by cholestyramine. Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

ADVERSE REACTIONS

Hypertension

The following potentially serious adverse reactions have been reported rarely with DIOVAN® and DIOVAN®-HCT: syncope, hypotension. In pivotal trials, discontinuation due to Adverse Experiences (AE) occurred in 3.1% for DIOVAN® monotherapy and 4.0% for placebo; and in 2.4% for DIOVAN®-HCT and 4.3% for placebo.

The following tables include adverse events with an incidence of ≥ 1% in the active treatment group, irrespective of causal relationship to study drug.

DIOVAN® monotherapy 80 to 160 mg/day†

	DIOVAN® (n = 2827) %	Placebo (n = 1007) %
Headache	8.5	13.6
Dizziness	2.8	3.9
Upper Respiratory Tract Infection	2.9	2.3
Coughing	2.7	1.3
Rhinitis	1.8	2.0
Sinusitis	1.5	1.7
Pharyngitis	1.3	0.7
Bronchitis	1.1	1.3
Diarrhea	2.5	1.6
Abdominal Pain	1.3	0.9
Nausea	1.5	2.2
Dyspepsia	1.1	1.8
Arthralgia	1.3	0.9
Back Pain	2.2	1.5
Fatigue	1.9	1.3
Viral Infection	3.1	2.6

DIOVAN®-HCT 80 mg/12.5 mg, 80 mg/25 mg, 160 mg/12.5 mg and 160 mg/25 mg

	DIOVAN®-HCT (n = 2066) %	Placebo (n = 93) %
Fatigue	2.0	1.1
Chest Pain NEC	1.1	1.1
Headache NOS	5.1	17.2
Dizziness (excl. Vertigo)	3.9	6.5
Sinusitis NOS	1.3	3.2
Nasopharyngitis‡	2.7	1.1
URT Infection	1.4	2.2
Coughing	1.4	0.0
Diarrhea NOS	1.2	0.0
Nausea	1.0	1.1
Back Pain	1.5	3.2
Pain in Limb§	1.1	0.0

† No AE appeared to have an incidence related to dose
‡ Nasopharyngitis including pharyngitis and rhinitis
§ Pain in Limb including arm pain and leg pain

NEC = Not elsewhere classified; NOS = Not otherwise specified

In a study conducted with patients taking DIOVAN® at starting doses of 20 mg to 320 mg, an increased incidence of dizziness was observed with DIOVAN® 320 mg (9%) compared to DIOVAN® 20 to 160 mg (2 to 4%). In another study where patients were up-titrated to the 320 mg dose of DIOVAN®, the incidence of dizziness was comparable to the 160 mg dose (1%).

In double-blind controlled trials with DIOVAN® alone, the following adverse events were reported at an occurrence rate of less than 1% regardless of drug relationship: orthostatic effects, chest pain, palpitations, myalgia, asthenia, somnolence, vertigo, impotence, epistaxis, fibrosing alveolitis (one case), allergic reactions, urticaria, pruritus and rash.

In controlled clinical trials of DIOVAN®-HCTZ, the incidence of patients with decreases in serum potassium and increases in BUN were dose related, occurring more frequently in patients receiving the combination doses with HCTZ 25 mg compared to HCTZ 12.5 mg.

Dose-related orthostatic effects were seen in < 1% of patients receiving DIOVAN®-HCTZ. A dose-related increase in the incidence of dizziness was observed in patients treated with DIOVAN®/HCTZ 80/12.5 mg to 160/25 mg. Fatigue, vertigo, and arthralgia occurred more frequently with DIOVAN®/HCTZ 160/25 mg than 160/12.5 mg.

Following Myocardial Infarction

The following table shows the frequency of selected serious adverse events (≥ 0.4% on any treatment group) for the DIOVAN®, DIOVAN® + Captopril and captopril treatment groups in a large, randomized double-blind trial. Serious adverse events related to the disease under study are not included in this table.

Selected serious adverse events by treatment (safety population)

	DIOVAN® (n = 4885) %	DIOVAN® + Captopril (n = 4862) %	Captopril (n = 4879) %
Hypotension [1]	2.8	3.9	2.8
Syncope	0.7	0.6	0.6
Dizziness	0.4	0.4	0.3
Renal causes [2]	3.1	3.0	2.0
Hyperkalemia	0.4	0.6	0.4
Atrial fibrillation	1.0	0.7	0.8
Cough	0.3	0.5	0.4
Taste disturbances [3]	0.1	0.4	0.3

[1] This term includes SAEs related to hypotension, orthostatic hypotension.
[2] This term includes SAEs related to acute renal failure, chronic renal failure, blood creatinine increased.
[3] This term includes ageusia, dysgeusia, hypogeusia.

Major renal dysfunction was observed in 3.8%, 3.7%, and 2.6% of patients in the DIOVAN®, DIOVAN® + captopril, and captopril treatment groups, respectively. Major renal dysfunction was defined as death from a renal cause, a serious adverse event suggestive of renal failure, and temporary or permanent discontinuation of study drug for a renal cause.

Post-Marketing Experience

Other adverse reactions reported rarely in post-marketing use include: anaphylaxis (very rarely), angioedema (involving swelling of the face, lips and/or tongue), photosensitivity, increase in blood pressure and taste disorders. Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Laboratory Findings

Occasional elevations of liver enzymes occurred in DIOVAN®-HCT treated patients.

Hypertension

	DIOVAN® %	Placebo %
Hyperkalemia: > 20% increase in serum potassium	5.0	3.0
Creatinine: minor elevation	1.1	0.8
Hemoglobin: > 20% decrease	0.4	0.1
Hematocrit: > 20% decrease	0.8	0.1
Neutropenia¶	1.9	0.5

	DIOVAN®-HCT %	Placebo %
Creatinine: minor elevation	1.4	1.1
Hemoglobin: > 20% decrease	0.1	0.0
Hematocrit: > 20% decrease	1.0	0.0
Neutropenia	0.6	0.0

	DIOVAN® %	DIOVAN® + HCTZ %	HCTZ %	Placebo %
Elevation of uric acid levels	2.6	8.2	6.0	2.3

¶ In controlled clinical trials, thrombocytopenia was observed in 0.1% of patients.

Post-MI

	DIOVAN® %	DIOVAN® + Captopril %	Captopril %
Hyperkalemia: > 20% increase in serum potassium	2.3	2.4	1.5
Doubling of serum creatinine	4.2	4.8	3.4

DOSAGE AND ADMINISTRATION

DIOVAN® monotherapy

Hypertension

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors (see WARNINGS, Hypotension). The dosage of antihypertensive agents used with DIOVAN® may need to be adjusted. The recommended initial dose of DIOVAN® is 80 mg once daily. The antihypertensive effect is present within 2 weeks and maximal reduction is usually attained within 4 weeks following initiation of therapy. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to a maximum of 320 mg or a thiazide diuretic added. It is not recommended to prescribe the maximum dose of 320 mg without prior up-titration. DIOVAN® should be administered consistently with or without food.

Following Myocardial Infarction

DIOVAN® may be initiated as early as 12 hours after a myocardial infarction in clinically stable patients. In order to diminish the risk of hypotension, the recommended starting dose is 20 mg twice daily. Thereafter, patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to dosage reduction. DIOVAN® should be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin and statins, as indicated. Concomitant use of beta-blockers is to be encouraged with DIOVAN® in this clinical setting, if indicated, since further substantial relative risk reduction may be expected with such use over that of DIOVAN® alone.

DIOVAN®-hydrochlorothiazide

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of DIOVAN®-HCT should be determined by the titration of the individual components.

Once the patient has been stabilized on the individual components as described below, DIOVAN®-HCT tablet, 80 mg/12.5 mg, 160 mg/12.5 mg, or 160 mg/25 mg once daily may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination. DIOVAN®-HCT may be administered with or without food, however it should be taken consistently with respect to food intake.

Hepatic Impairment

No initial dosage adjustment in DIOVAN® is required in patients with mild to moderate liver disease (see PRECAUTIONS). Patients with Impaired Liver Function). Care should be exercised in patients with liver disease. However, because thiazide diuretics may precipitate hepatic coma, care should be exercised when administering a fixed combination product containing hydrochlorothiazide.

Renal Impairment

No initial dosage adjustment is required for patients with renal impairment including those patients requiring hemodialysis. Appropriate monitoring of these patients is recommended. The usual regimens of therapy with DIOVAN®-HCT may be followed if the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so DIOVAN®-HCT is not recommended.

Elderly

No dosage adjustment is usually necessary however see PRECAUTIONS, Use in the Elderly.

Concomitant Diuretic Therapy

In patients receiving diuretics, DIOVAN® therapy should be initiated with caution, since these patients may be volume-depleted and more likely to experience hypotension following initiation of additional antihypertensive therapy. When possible, all diuretics should be discontinued two to three days prior to administration of DIOVAN® to reduce the likelihood of hypotension (see WARNINGS, Hypotension, and PRECAUTIONS, Drug Interactions). If this is not possible, DIOVAN® should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Stability and Storage Recommendations

Protect from moisture and heat (store at 15-30°C).

AVAILABILITY OF DOSAGE FORMS

DIOVAN® 40 mg, 80 mg, 160 mg and 320 mg tablets are supplied in cartons containing 2 blister strips of 14 tablets. Since the 40 mg tablets are scored on one side, these may be used to initiate therapy following myocardial infarction (see DOSAGE AND ADMINISTRATION, Following Myocardial Infarction).

DIOVAN®-HCT tablets, 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, are supplied in cartons containing 2 blister strips of 14 tablets.

References:

1. Diovan® Product Monograph. Novartis Pharmaceuticals Canada Inc., December 12, 2006.
2. Diovan®-HCT Product Monograph. Novartis Pharmaceuticals Canada Inc., October 14, 2005.

NOVARTIS

Novartis Pharmaceuticals Canada Inc.

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PMAC PQAD

Le Médecin de famille canadien (septembre 2007)

RELENZA®

ZANAMIVIR

Prescribing Summary

IMPORTANT: For complete prescribing information, please refer to the full Product Monograph at www.gsk.ca

Patient Selection Criteria

INDICATIONS AND CLINICAL USE

Treatment of Influenza: RELENZA® (zanamivir) dry powder for inhalation is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older, who have been symptomatic for no more than 2 days. No data are available to support RELENZA® safety and efficacy in patients who receive treatment after 48 hours of symptoms. This indication is based on placebo-controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used. RELENZA®, when taken as recommended for treatment of influenza, alleviates the symptoms and reduces their duration.

Prophylaxis of Influenza: RELENZA® is indicated in adults and pediatric patients 7 years of age and older for prophylaxis of influenza.

Important Information on Use of RELENZA®

RELENZA® is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm. RELENZA® has not been proven effective for prophylaxis of influenza in the nursing home setting. RELENZA® is not a substitute for influenza vaccination on an annual basis as recommended by the National Advisory Committee on Immunization (NACI).

CONTRAINDICATIONS

RELENZA® is contraindicated in patients with a known or suspected hypersensitivity to RELENZA® or any component of the zanamivir inhalation powder (including lactose, which contains milk protein).

Special Populations

Pregnant Women: The safe use of RELENZA® during pregnancy has not been established. There are no adequate and well controlled studies of RELENZA® in pregnant women. There is no information on placental transfer in humans. Reproductive studies performed in rats and rabbits indicated that placental transfer of RELENZA® occurs. In these animals, fetal blood concentrations of RELENZA® were significantly lower than concentrations of RELENZA® in the maternal blood. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or malformations. One embryo/fetal study, was conducted using subcutaneous administration of RELENZA®, 3 times daily at doses of 1, 9 or 80 mg/kg during days 7 to 17 of pregnancy. Based on AUC measurements, the high dose in the study produced an exposure greater than 1000 times the human exposure at the proposed clinical dose. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. The individual incidence rates of each skeletal alteration or variant, in many but not in all cases, remained within the range of background rates of the historical occurrence in the rat strain studied. RELENZA® should not be used in pregnancy, especially during the first trimester, unless the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

Nursing Women: Studies in rats have demonstrated that RELENZA® is excreted in milk. Nursing mothers, however, should be instructed that it is not known whether RELENZA® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELENZA® is administered to a nursing mother.

Pediatrics: Safety and effectiveness of RELENZA® for treatment of influenza have not been established in pediatric patients under 7 years of age. Safety and effectiveness of RELENZA® for prophylaxis of influenza have not been assessed in pediatric patients under 5 years of age. Efficacy data from the age of 5 to 7 years are limited. Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of RELENZA® is considered. When RELENZA® is prescribed for children, it should be used only under adult supervision and with attention to proper use of the delivery system.

Geriatrics (≥65 years of age): At the therapeutic daily dose of 20 mg, bioavailability of RELENZA® in young healthy adults is low (10-20%), and as a result systemic exposure of patients to RELENZA® is limited. The bioavailability of RELENZA® in elderly individuals has not been determined. However, a total of 83 elderly patients (aged ≥65 years old) received inhaled RELENZA® at a dose of 10 mg twice daily, or greater, for the treatment of symptomatic influenza in completed clinical trials. Of the total number of patients who received RELENZA® 10 mg once daily for prophylaxis of influenza in households and community settings in 4 clinical studies of RELENZA®, 954 were aged 65 and over. The safety profile did not appear to vary with increasing age and no overall differences in the safety and efficacy were observed between the elderly and younger patients. However, greater sensitivity of some older patients to medications in general, cannot be ruled out. In 2 additional studies of RELENZA® for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated. Elderly subjects may need assistance with use of the device.

Safety Information

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

There have been reports of patients being treated for influenza who have experienced bronchospasm and decline in respiratory function. Many but not all of these patients had underlying airways disease such as asthma or chronic obstructive pulmonary disease. There have been cases of respiratory arrest, including deaths, in which a contribution from RELENZA® cannot be excluded. RELENZA® should be discontinued in any patient who develops bronchospasm or a decline in respiratory function; immediate treatment and hospitalization may be required. All patients should be advised of the risk of bronchospasm with RELENZA®.

RELENZA® is not generally recommended for treatment of patients with severe underlying airways disease because of the risk of serious adverse events and because efficacy has not been demonstrated in this population.

General Due to the limited number of patients with severe asthma or other severe chronic respiratory diseases, patients with chronic illnesses or immunocompromised patients who have been treated, it has not been possible to demonstrate the efficacy and safety of RELENZA® in these groups.

Vaccination of persons at high risk each year before the influenza season is currently recognized as the most effective measure for reducing the impact of influenza. The use of RELENZA® should not affect the evaluation of individuals for annual influenza vaccination, in accordance to *"Health Canada, An Advisory Committee Statement, National Advisory Committee on Immunization (NACI), Statement on Influenza Vaccination for the current Year/Season"*.

Patients should be instructed in the use of the DISKHALER® inhalation device and instructions should include a demonstration wherever possible. Patients should be advised to read and follow carefully the patient instructions to ensure safe and effective use. Patients should be advised to finish the full course of treatment or prophylaxis therapy as prescribed.

Hepatic/Biliary/Pancreatic: The pharmacokinetics of RELENZA® have not been investigated in patients with impaired hepatic function; doses of up to 1200 mg IV in healthy adults did not show evidence of hepatic metabolism.

Immune: Serious bacterial infections may begin with influenza-like symptoms or may co-exist with or occur as complications during the course of influenza. RELENZA® has not been shown to prevent such complications.

Renal: At the therapeutic daily dose of 20 mg, bioavailability is low (10-20%), and as a result systemic exposure of patients to RELENZA® is limited. However, after a single IV dose of 4 mg or 2 mg of RELENZA® in volunteers with mild or moderate, or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/h, mild/moderate 2.7 L/h, and severe 0.8 L/h; median values) and significant increases in half-life (normals 3.1 h, mild/moderate 4.7 h, and severe 18.5 h; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency after repeated dosing.

Respiratory: Safety and efficacy of RELENZA® have not been demonstrated in patients with severe underlying chronic pulmonary disease or severe asthma due to limited number of patients treated. Therefore, RELENZA® is not generally recommended for treatment in such patients. Serious adverse events have been reported in patients with underlying chronic pulmonary disease and in patients with severe or decompensated chronic obstructive pulmonary disease or asthma.

If treatment with RELENZA® is considered for a patient with underlying airway disease, the potential risks and benefits should be carefully weighed. The patients should be advised of the risk of bronchospasm. If a decision is made to prescribe RELENZA® for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation and appropriate supportive care including availability of fast-acting bronchodilators. Patients should be instructed to contact their physician if they experience increased respiratory symptoms during treatment such as worsening wheezing, shortness of breath, or other signs or symptoms of bronchospasm and to discontinue RELENZA®. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA® should be advised to use their bronchodilators before taking RELENZA®.

In a placebo controlled study in patients with predominantly mild/moderate asthma and/or Chronic Obstructive Pulmonary Disease (COPD), RELENZA® was shown to be effective and well tolerated for the treatment of influenza. There was no evidence of a difference between RELENZA® and placebo in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) measured after the end of treatment.

Sensitivity/Resistance: Allergic-like reactions, including facial and oropharyngeal oedema, bronchospasm, laryngospasm, dyspnoea, urticaria, serious skin rashes and anaphylaxis have been reported in post-marketing experience. RELENZA® should be discontinued and immediate medical attention sought by any patient who develops an allergic reaction or if one is suspected.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because the placebo consisted of inhaled lactose powder which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Treatment of Influenza

Clinical studies were conducted predominately in young adults, in pediatric patients 5 to 12 years old, and in high risk patients (mostly patients with underlying respiratory disease and/or elderly ≥65 years old). The incidence of adverse events in these trials appeared similar in the RELENZA® and placebo groups. No differences in adverse reactions were observed between these patient groups.

Adverse events that occurred with an incidence ≥1.5% in treatment studies in adults and adolescents are listed in Table 1.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA® and placebo included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria. Other side effects that have been reported, but are not as common include allergic reactions and rashes. Adverse events that occurred with an incidence ≥1.5% in children receiving treatment doses of RELENZA® in two Phase 3 studies are listed in Table 2.

Prophylaxis of influenza

Family/Household Prophylaxis Studies: Adverse events that occurred with an incidence of ≥1% in the 2 prophylaxis studies are listed in Table 3. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA® 10 mg or placebo inhaled once daily for 10 days.

Community Prophylaxis Studies: Adverse events that occurred with an incidence of ≥1% in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥12 years of age receiving RELENZA® 10 mg or placebo inhaled once daily for 28 days.

Abnormal Hematologic and Clinical Chemistry Findings

The most frequent laboratory abnormalities in Phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of RELENZA® and lactose vehicle placebo recipients with acute influenza-like illness.

Post-Market Adverse Drug Reactions

Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

The following adverse events have been reported spontaneously during post-marketing experience with RELENZA®. However, a causal relationship to RELENZA® cannot be clearly established for spontaneously reported events.

Cardiac: Arrhythmias, syncope, tachycardia

Gastrointestinal: Diarrhea, nausea, vomiting

General: Allergic or allergic-like reactions, including facial and oropharyngeal oedema, laryngospasm

Neurologic: Dizziness, headaches, insomnia, seizures

Respiratory: Bronchospasm, dyspnea

Skin: Rash, including serious cutaneous reactions, and urticaria

To report an adverse event, you may notify Health Canada by phone at 1-866-234-2345, by Toll-free fax at 1-866-678-6789 or by Email at cadrmp@hc-sc.gc.ca

DRUG INTERACTIONS

Drug-Drug Interactions: RELENZA® is less than 15% protein bound. There is no evidence of hepatic metabolism, and

Advertising with Product Claim PI Format

- Follow code instructions s7.3
- FAQs on web-site
- Font size
- Can adjust font style
- Can edit PI while maintaining PM content message e.g.

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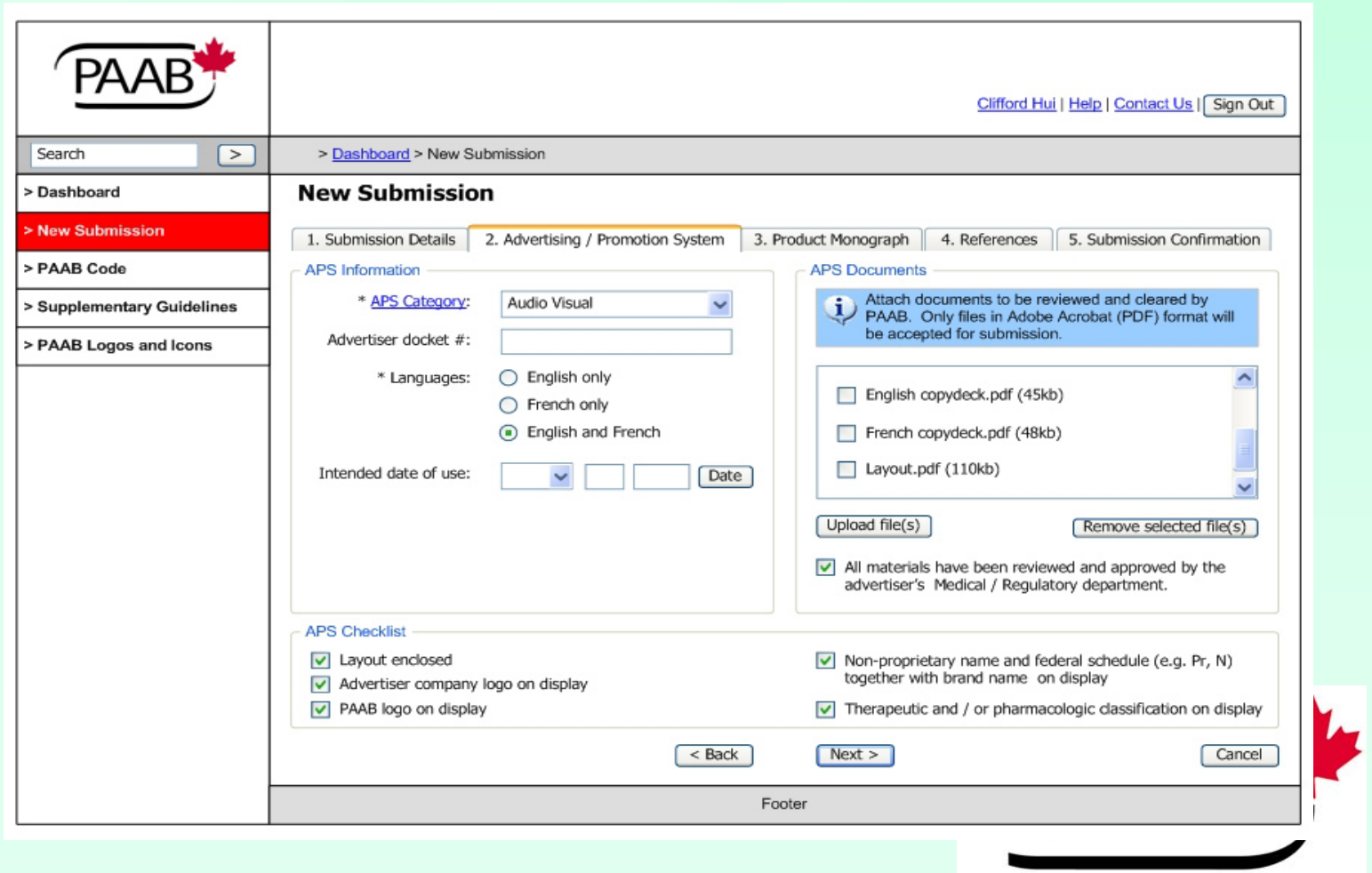
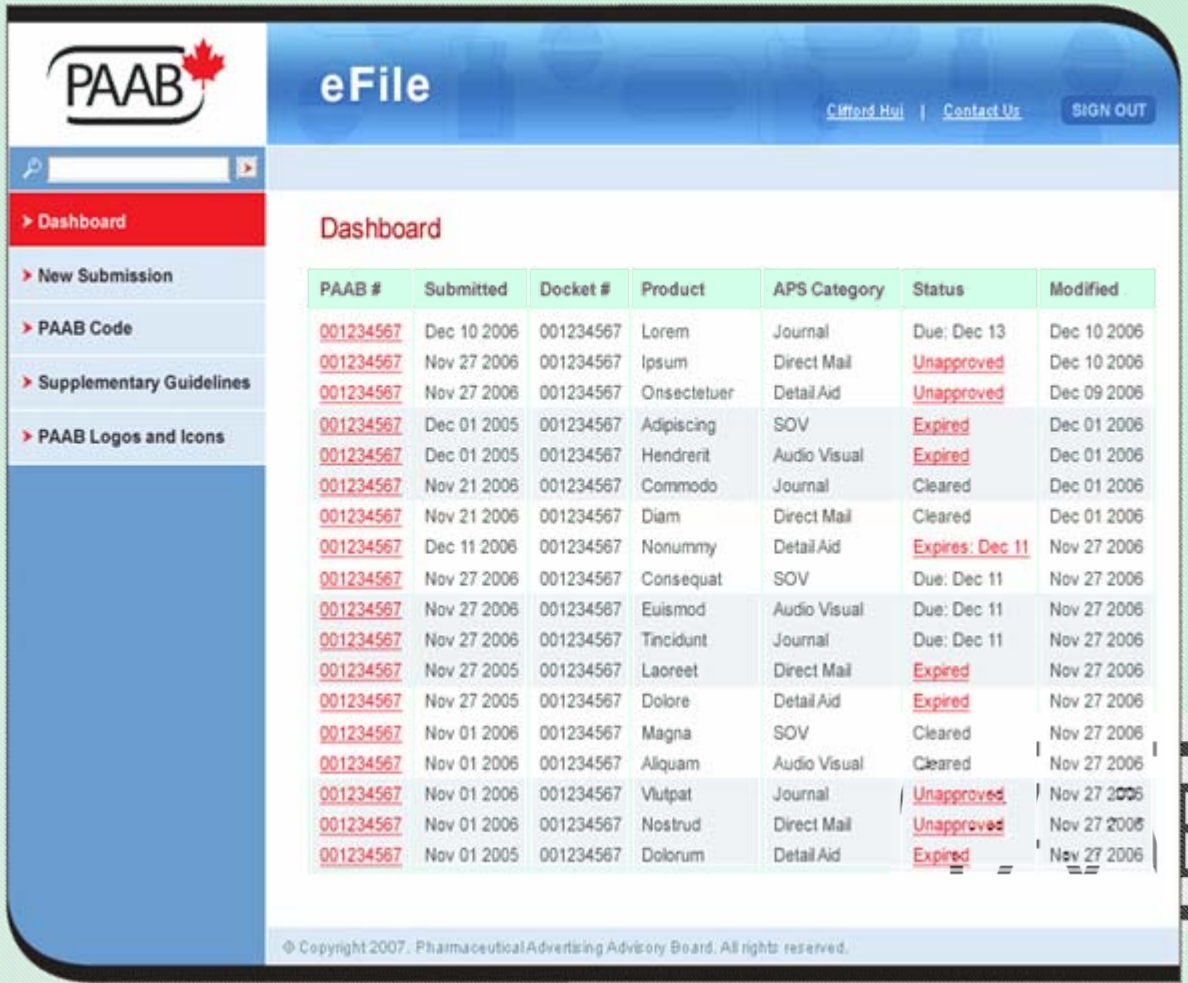
Provide information about the submitter, the organization and the product

Upload the PDF documents & indicate the intended use



Agency Dashboard

- Provide an “at a glance” view of all submissions
- Order by submission status



How to Get to Approval Fast

- Ensure that Med/Reg Dept review the ad prior to sending to PAAB (s2.9)
- Quote PAAB back files
- Highlight the source in the reference
- Notify reviewers of any additional changes in the ad
- Make changes to all affected pages

Fast Approval (continued)

- Consider issue of fair balance type-size at early stage
- Review the PAAB comments
- Call reviewers if necessary to clarify issues
- Ensure that references used comply with the PAAB Code (s3.1, 3.2)

Pre-NOC Review Policy

- Product Monograph at final draft
- Ask if meeting will help PAAB review
- max. 2 core APS
- Turnaround at discretion of the PAAB
- See complete guideline at:

  www.paab.ca

Trust

The image of the pharmaceutical industry has declined over the past decade which has resulted in an atmosphere of distrust regarding the intentions, motivation and information provided by pharmaceutical companies to help consumers and professionals.

U.S. Experience

- $5+ billion in fines and criminal penalties
- OIG, DOJ, FDA, FBI, state AGs, FTC, SEC
- PhRMA guidelines & DTCA restrictions
- new state laws imposing compliance
- DOJ, Congress, States after CME re off label
- 150+ qui tam cases under seal
- ACCME guidelines on commercial support
- Senate Finance Committee

PAAB

Is it reasonable to assume you have a choice to obey the law?

- May 1999 – Genentech -$50 million
- January 2001 – Bayer - $14 M
- September 2001 – TAP -$870 M
- October 20002 – Pfizer $49 M
- April 2003 – Bayer -$257 M
- June 2003 - GSK $90 M & AstraZeneca $355 M
- July 2003 Abbott Laboratories - $600 M
- May 2004 – Parke Davis - $430 M
- June 2004 – Schering Plough - $345 M
- May 2005 – TAP $150 M
- September 2005 – GSK $150 M
- October 2005 - Serono $740 M
- December 2005 - King Pharmaceuticals -$124 M
- February 2006 – Eli Lilly $36 M
- August 2006 – Schering Plough - $435 M
- October 2006 – Intermune - $36.9 M

PAAB

Thank You

PAAB