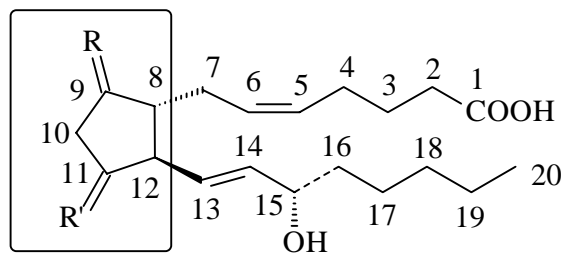


## Prostaglandins and the Eicosanoids

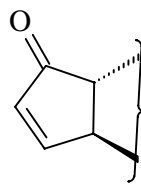
### I. Introduction and Structure

The eicosanoids (specifically the prostaglandins) were discovered in 1935 when a Swedish physiologist and Nobel laureate, Ulf von Euler, and other investigators found that extracts of seminal vesicles or of human semen lowered blood pressure and caused contraction of strips of uterine tissue. Von Euler coined the term prostaglandin because he assumed that the active material came exclusively from the prostate gland.

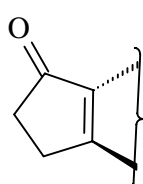
Eicosanoids are 20-carbon fatty acids that are produced in a variety of tissues and that mediate an array of physiologic and pathologic processes (see Table at end of this Chapter and Pharmacology Notes). They consist of the prostaglandins PGA through PGH, which are present in nearly all mammalian tissues where they regulate function; the related thromboxanes, which are found in blood platelets; and the leukotrienes, whose biological effects include respiratory, vascular, and intestinal activities. All of the eicosanoids are derived from the oxidative metabolism of arachidonic acid (5, 8, 11, 14-eicosatetraenoic acid) through what is referred to as the “arachidonic acid cascade”.



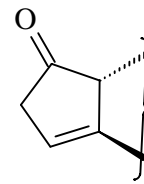
**Protenoic Acid**



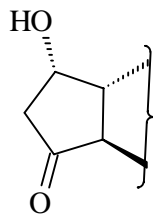
**PGA2**



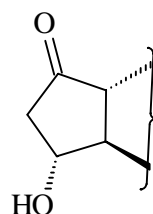
**PGB2**



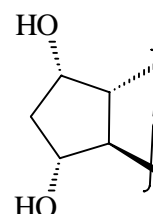
**PGC2**



**PGD2**



**PGE2**



**PGF2**

Prostaglandins (PGs) consist of an oxygenated cyclopentane/pentene ring with a heptenoic or heptanoic acid side and a octenol side chain on adjacent carbon atoms of the ring. This basic structural unit is referred to as a prostanoic or protenoic acid. Each PG

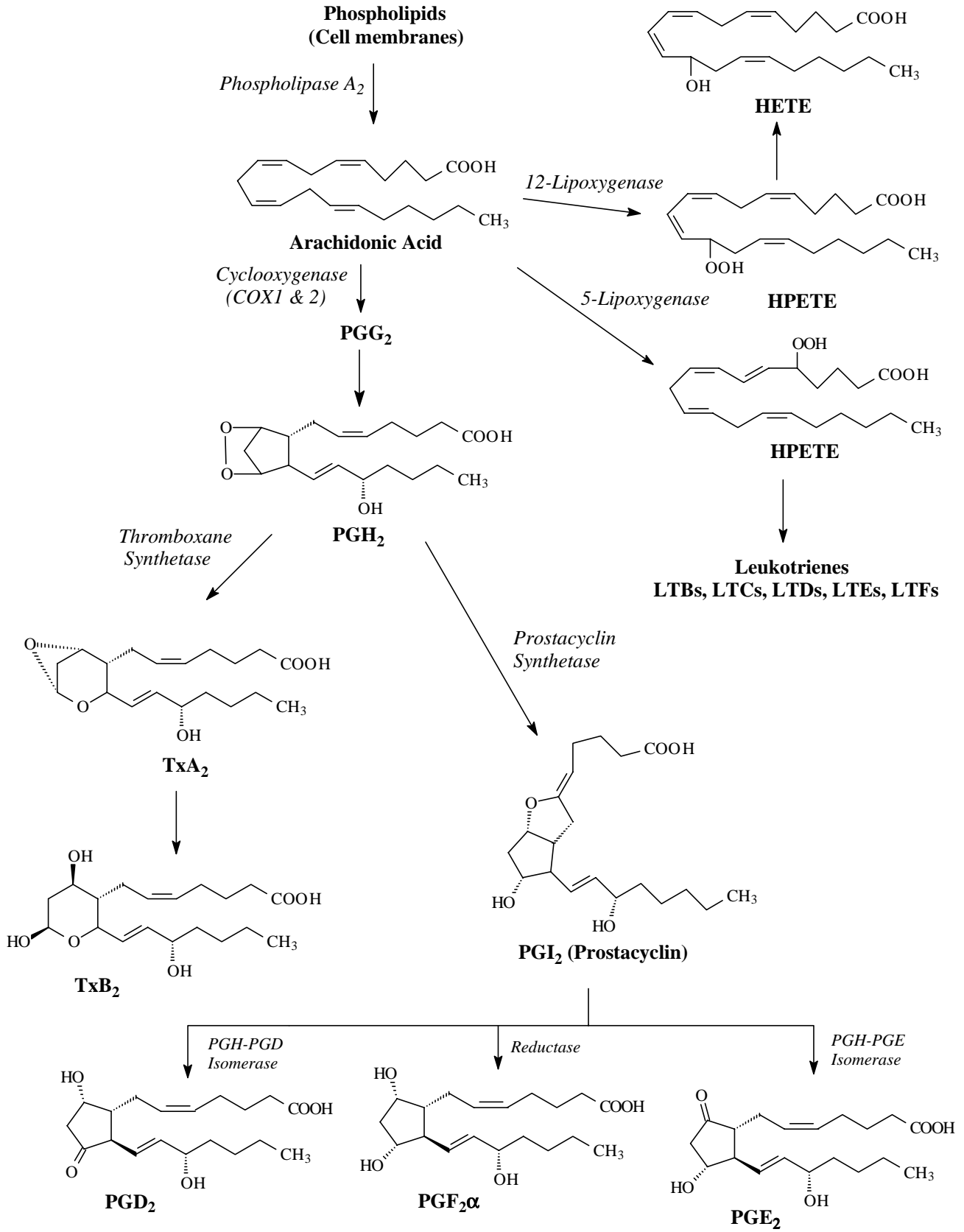
differs from the others in the substitution pattern in the cyclopentane ring and the side-chains and these differences are responsible for the different biologic activities of the members of the prostaglandin group. Prostaglandins are broadly classified as PGA, PGB, PGC, PGD, PGE, PGF, PGG, and PGH based on their cyclopentane/pentene ring substitution patterns. Each general PG class is subclassified based on the degree of unsaturation (i.e. PGE<sub>1</sub>, PGE<sub>2</sub>, PGF<sub>2</sub>). The letters and numbers that follow the initial PG abbreviation indicate the nature of the unsaturation and substitution. For example, the subscript 1 in PGE<sub>1</sub> indicates one double bond in the side chains, while the subscript 2 in PGE<sub>2</sub> indicates two double bonds in the side chains (see Biosynthesis Section and Drug monographs that follow). The thromboxanes (also prostanoids) and leukotrienes are also sub-classified based on substitution patterns and degree of substitution as shown below.

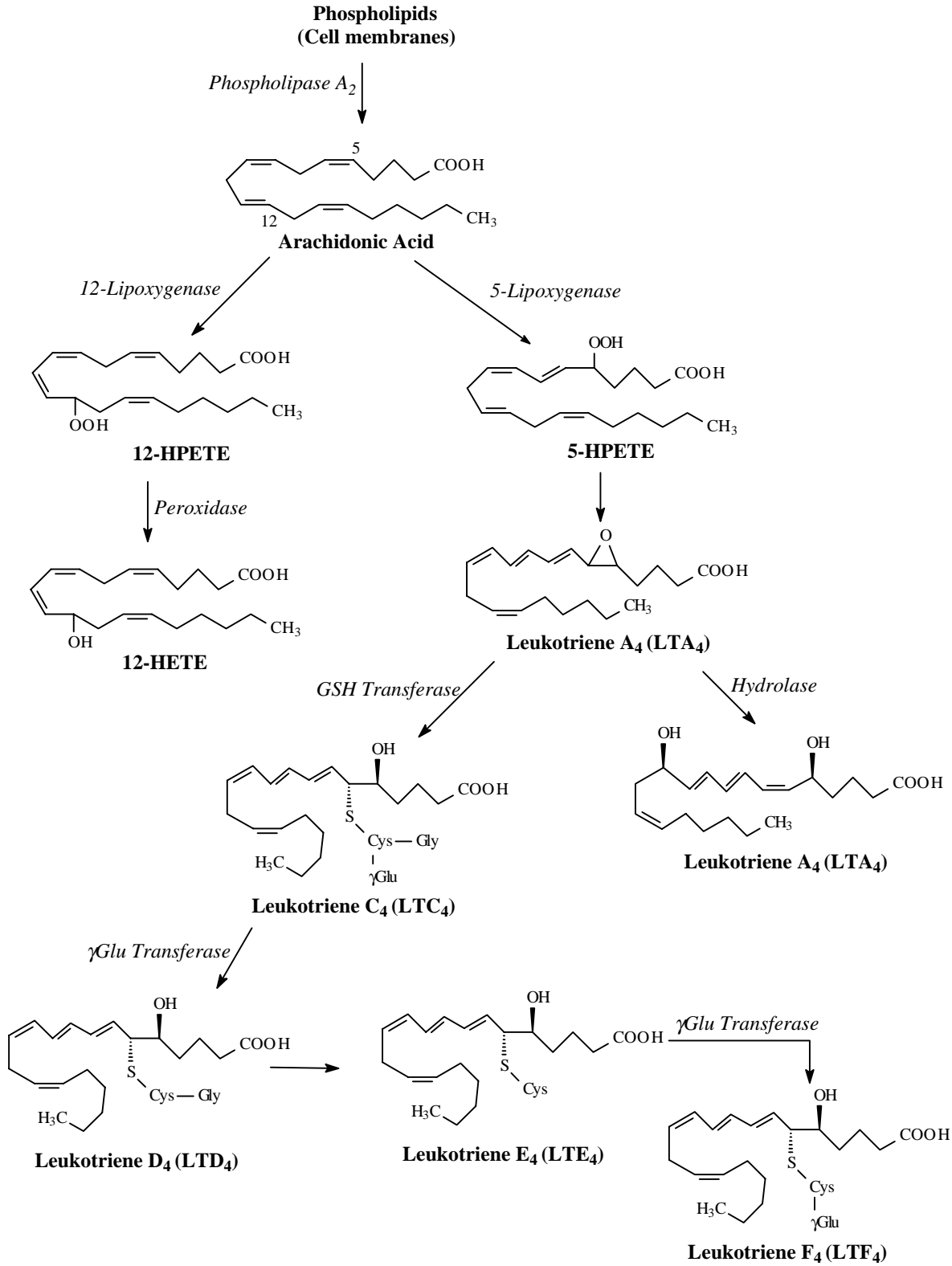
## II. Eicosanoid Biosynthesis

The key precursor in eicosanoid biosynthetic pathways is arachidonic acid that is formed from linolenic acid through reactions catalyzed by a series of enzymes that dehydrate fatty acids. Cells store arachidonic acid as a component of membrane phospholipids such as phosphoinositol. In response to an appropriate stimulus, arachidonic acid is liberated from the storage lipid by an enzymatic reaction catalyzed by phospholipase A<sub>2</sub>. There are a number of drugs, such as the glucocorticoids, that modulate PLA<sub>2</sub> and thereby influence (inhibit) eicosanoid production. The conversion of free arachidonic acid to prostaglandins and other eicosanoids is initiated oxidative enzymes of the cyclooxygenase (PGH-synthase) and lipoxygenase families.

Cyclooxygenase stereospecifically adds two molecules of oxygen to arachidonic acid to form the unique bicyclic endoperoxide PGG<sub>2</sub>. The hydroperoxide group of PGG<sub>2</sub> is then reduced by the cyclooxygenase (PGH-synthase) to yield the single 15(S)-alcohol PGH<sub>2</sub>. Two different isozymes of cyclooxygenase exist, a constitutive form (COX-1) and a highly inducible form (COX-2). The COX isozymes are variably inhibited by ω<sub>3</sub>-fatty acids (eicosapentaenoic acid and docosahexaenoic acid) as well as the traditional NSAID drugs and the COX-2 inhibitors. The structure and inhibition of COX isozymes are discussed in more detail in the NSAID Chapter. PGH<sub>2</sub> serves as a “branch point” for specific enzymes leading to the formation of prostacyclin (PGI<sub>2</sub>), the various prostaglandins as well as the thromboxanes. Which derivatives form from PGH<sub>2</sub> is determined by specific tissues and their metabolic capabilities and physiologic functions as discussed in the next section.

The lipoxygenase pathway of arachidonic acid metabolism produces a variety of acyclic lipid peroxides (hydroperoxyeicosatetraenoic acids or HPETEs) which can be reduced to the corresponding alcohols (hydroxyeicosatetraenoic acids or HETEs). The HPETEs can yield the oxirane (epoxide) LTA<sub>4</sub> which may be hydrolyzed to LTB<sub>4</sub> or conjugated with glutathione to yield LTC<sub>4</sub>. Modification of the glutathione conjugate amino acids by hydrolysis yields the other leukotrienes LTD<sub>4</sub>, LTE<sub>4</sub> and LTF<sub>4</sub>. The roles of various leukotrienes are summarized in the section that follows.





### III. Physiologic Actions of the Eicosanoids

The prostaglandins are important mediators of normal physiologic events and have been implicated in a variety of pathologies. They have been implicated in inflammation, pain, pyrexia, cardiovascular disease, renal disease, cancer, glaucoma, allergic rhinitis, asthma preterm labor, male sexual dysfunction and osteoporosis. This has led to the development of a number of prostaglandin drug products as indicated in the Table below and discussed in more detail in the following chapters.

#### Prostaglandin Drug Products Used Worldwide (*Major US products in Italics*)

<b>Prostaglandin Drug</b>	<b>General Therapeutic Indication</b>
<i>Carboprost trometamol</i>	<i>Abortifacient</i>
Gemeprost	Abortifacient
Sulprostone	Abortifacient
<i>Dinoprostone (PGE<sub>2</sub>)</i>	<i>Child Birth</i>
<i>Alprostadil (PGE<sub>1</sub>) – many products</i>	<i>Male sexual dysfunction and Peripheral vascular disease</i>
<i>Beroprost</i>	<i>Peripheral vascular disease</i>
Iloprost	Peripheral vascular disease
<i>Epoprostenol</i>	<i>Pulmonary Hypertension</i>
<i>Treprostinil</i>	<i>Pulmonary Hypertension</i>
<i>Misoprostol</i>	<i>Ulcers</i>
Enoprostil	Ulcers
Omoprostil	Ulcers
Limaprost	Buerger's Disease
<i>Latanoprost</i>	<i>Glaucoma</i>
<i>Unoprostone isopropyl</i>	<i>Glaucoma</i>
<i>Travoprost</i>	<i>Glaucoma</i>
<i>Bimatoprost</i>	<i>Glaucoma</i>
Arthrotec	Arthritis

Prostaglandin effects are usually manifested locally around the site of prostaglandin synthesis (paracrine) and their actions are multiple and variable (stimulatory or inhibitory) depending on tissue type and the nature of the receptors with which they interact. To date eight prostanoid receptors have been cloned and characterized. Note that these receptors are coupled to either phospholipase C (PLC) or adenylate cyclase (AC) and, in the case of adenylate cyclase, the action of the PGs may be stimulatory or inhibitory.

The physiologic actions of various eicosanoids are summarized in the Table at the end of this section. Prostaglandins are powerful vasodilators; that is, they relax the muscles in the walls of blood vessels so that the diameters become larger and there is less resistance to the flow. Consequently, the blood pressure falls. Again, the effect can be local. An important example of the vasodilation effect of prostaglandins is in the kidney, where widespread vasodilation leads to an increase in the flow of blood to the kidney and an

increased excretion of salt in the urine. Thromboxanes, on the other hand, are powerful vasoconstrictors in the same setting.

<b>PG Receptor</b>	<b>Endogenous Ligand</b>	<b>Signaling Pathway</b>
EP <sub>1</sub>	PGE <sub>2</sub>	Increased Ca <sup>++</sup> via PLC stimulation
EP <sub>2</sub>	PGE <sub>2</sub>	Increased cAMP via AC stimulation
EP <sub>3</sub>	PGE <sub>2</sub>	Decreased cAMP via AC inhibition
EP <sub>4</sub>	PGE <sub>2</sub>	Increased cAMP via AC stimulation
FP	PGF <sub>2α</sub>	Increased Ca <sup>++</sup> via PLC stimulation
DP	PGD <sub>2</sub>	Increased Ca <sup>++</sup> via PLC stimulation
IP	PGI <sub>2</sub>	Increased Ca <sup>++</sup> via PLC stimulation
TP	TxA <sub>2</sub>	Increased Ca <sup>++</sup> via PLC stimulation

Some diuretics, such as furosemide, may act in part by releasing prostaglandins in the kidney. Prostaglandins inhibit the action of vasopressin on the kidney tubules, resulting in enhanced urinary excretion of water. The resultant tendency to dehydration from this enhanced excretion of water leads to local secretion of another kidney prostaglandin that stimulates the secretion of renin. Renin stimulates the production of aldosterone, which has the affect of conserving sodium and water, thus combating the dehydration and elevating the depressed blood pressure. Although prostaglandins were first detected in semen, no biologic role for them has been defined in the male reproductive system. This is not true, however, for females. It has been shown that prostaglandins mediate the control of GnRH over LH secretion, modulate ovulation, and stimulate uterine muscle contraction. Discovery of this last property has led to the successful treatment of menstrual cramps (dysmenorrhea) through the use of NSAIDs as inhibitors of prostaglandin synthesis. Prostaglandins also play a role in inducing labor in pregnant women at term or in inducing therapeutic abortions.

The process of clot formation begins with an aggregation of blood platelets. This process is strongly stimulated by thromboxanes and inhibited by prostacyclin. Prostacyclin is synthesized in the walls of blood vessels and serves the physiological function of preventing needless clotting. Thromboxanes, on the other hand, are synthesized within the platelets themselves and are released. The platelets adhere to one another and to blood vessel walls. Through prostaglandin and thromboxane mechanisms, clotting is prevented when it is unnecessary and takes place when it is necessary. Platelets adhere in arteries that are affected by the process of atherosclerosis; they form plaques along the interior surface of the vessel wall. This type of platelet aggregation and clotting leads to blocking (occlusion) of the vessel wall, the most common cause of heart attack (coronary artery occlusion). This biologic insight has led to the widespread recommendation that those at risk for a coronary occlusion take aspirin, an inhibitor of the enzyme cyclooxygenase, daily as a preventive measure.

Eicosanoids, specifically the leukotrienes, also play a pivotal role in inflammation, a process characterized by the redness (rubor), heat (calor), pain (dolor), and swelling

(tumor). These changes are due to a local dilation of blood vessels that permits increased blood flow to the affected area. The blood vessels become more permeable, leading to the escape of infection-fighting fluid and white blood cells from the blood into the surrounding tissues. Thus, effective treatment to suppress inflammation in inflammatory but noninfectious diseases, such as rheumatoid arthritis, is to treat the patient with inhibitors of prostaglandin synthesis, such as aspirin. Similarly, the pain and fever of other disseminated inflammatory diseases can be alleviated by these nonsteroidal anti-inflammatory drugs.

The immune system protects from invasion by bacteria, viruses, or other noxious agents. It begins when a foreign substance is ingested by a mobile, scavenging, white blood cell, called a macrophage. The macrophage interacts with a special white blood cell called a T-lymphocyte (T cell), which in turn activates B-lymphocytes (B cells or plasma cells). The result is that the B cell elaborates and secretes specific proteins (antibodies) that are designed to make the ingested foreign invader more susceptible to attack and ingestion by other white blood cells. In cellular immune response, T cells become activated at the site of damage and release proteins called lymphokines, which attract macrophages to the local area and stimulate them to ingest the offending agents. Prostaglandins generally attenuate the immune response by inhibiting both T cell and B cell activity, but some prostaglandins, particularly the leukotrienes, enhance inflammatory responses.

Prostaglandins play important roles in the genesis of immune disorders, an awareness that has prompted investigation of inhibitors of prostaglandin synthesis for use in treatment of hypersensitivity (anaphylactic) reactions, allergies, and autoimmune diseases.

The functioning of the digestive tract is also influenced by prostaglandins. Depending on the setting, various prostaglandins may either enhance or inhibit the contraction of the smooth muscles of the intestinal walls. They are also powerful inhibitors of stomach secretions, perhaps because they inhibit the secretion of the stomach hormone gastrin, which stimulates gastric secretion. They also produce cytoprotective effects by enhancing GI blood flow and mucous and bicarbonate secretion. It is not surprising then that drugs like aspirin and the NSAIDs which inhibit prostaglandin synthesis may lead to peptic ulcers. Prostaglandin action on the digestive tract may cause a severe watery diarrhea and may mediate the effects of vasoactive intestinal polypeptide (VIP) in the Verner-Morrison syndrome (see above Hormones of the intestinal mucosa), as well as the effects of cholera toxin.

Prostaglandins induce several effects on endocrine function. Perhaps of greatest importance is the ability of prostaglandins to stimulate the resorption of bone in diseases such as rheumatoid arthritis and to cause hypercalcemia, particularly in patients harboring malignant tumors.

Prostaglandins and their therapeutic application include hydrocortisone and its synthetic derivatives, such as prednisone, which stabilize cell membranes and, in large doses, block the liberation of arachidonic acid. Drugs that inhibit prostaglandin synthesis include aspirin and the NSAIDs and acetaminophen. Anti-inflammatory steroids block the

production of eicosanoids by preventing the release of arachidonic acid from phospholipids. Nonsteroidal anti-inflammatory drugs, block enzymes that convert arachidonic acid to prostaglandins. Aspirin blocks different enzymes on alternative pathways so that the drugs can relieve inflammation brought on by different causes. The leukotrienes are also inflammatory agents. Drugs that block the enzymes that produce leukotrienes are effective treatments for asthma.

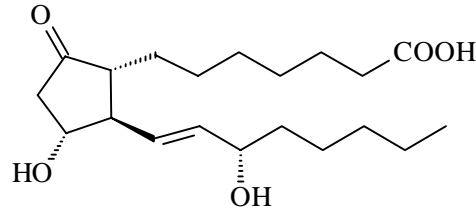
**Summary of the Physiologic Actions of the Eicosanoids**

<b>Eicosanoid</b>	<b>Biochemical and Physiologic Action</b>
PGD <sub>2</sub>	<ul style="list-style-type: none"> <li>• Weak inhibitor of platelet aggregation</li> </ul>
PGE <sub>1</sub>	<ul style="list-style-type: none"> <li>• Bronchial Vasodilation</li> <li>• Inhibitor of lipolysis</li> <li>• Inhibitor of platelet aggregation</li> <li>• <b>Contraction of GI smooth muscle</b></li> </ul>
PGE <sub>2</sub>	<ul style="list-style-type: none"> <li>• Stimulates hyperalgesic response (sensitize to pain)</li> <li>• Renal and bronchial vasodilation</li> <li>• Inhibitor of platelet aggregation</li> <li>• <b>Stimulates uterine smooth muscle relaxation</b></li> <li>• Cytoprotection: Protects GI epithelial cells from acid degradation</li> <li>• Reduces gastric acid secretion</li> <li>• Elevates thermoregulatory set-point in anterior hypothalamus (fever)</li> <li>• Promotes inflammation</li> </ul>
PGF <sub>2</sub>	<ul style="list-style-type: none"> <li>• Stimulates breakdown on corpus luteum (luteolysis): Animals</li> <li>• Stimulates uterine smooth muscle contraction</li> <li>• Bronchial constrictor</li> </ul>
PGI <sub>2</sub>	<ul style="list-style-type: none"> <li>• Potent inhibitor of platelet aggregation</li> <li>• Potent transient CV vasodilator, then vasodilator</li> <li>• Bronchial dilator</li> <li>• Uterine relaxant</li> <li>• Sensitize/amplify nerve pain response</li> </ul>
TXA <sub>2</sub>	<ul style="list-style-type: none"> <li>• Potent inducer of platelet aggregation</li> <li>• Potent vasoconstrictor (bronchioles, renal)</li> <li>• Decreases cAMP levels in platelets</li> <li>• Stimulates the release of ADP and 5-HT from platelets</li> </ul>
LTB <sub>4</sub>	<ul style="list-style-type: none"> <li>• Increases leukocyte chemotaxis and aggregation</li> </ul>
LTC/D <sub>4</sub>	<ul style="list-style-type: none"> <li>• Slow-reacting substance of anaphylaxis</li> <li>• Potent and prolonged contraction of ileal smooth muscle (Animals)</li> <li>• Contraction of lung parenchymal strips (Animals)</li> <li>• Bronchoconstriction in humans</li> <li>• Increased vascular permeability in skin (Animals)</li> </ul>
5- or 12-HPETE	<ul style="list-style-type: none"> <li>• Vasodilation of gastric circulation (Animals)</li> </ul>
5- or 12-PETE	<ul style="list-style-type: none"> <li>• Aggregates human leukocytes</li> <li>• Promotes leukocyte chemotaxis</li> </ul>



## Prostaglandins E and F as Therapeutic Agents in Reproduction

### I. Prostaglandin E<sub>1</sub> (Alprostadil)



Alprostadil (PGE<sub>1</sub>)

**Pharmacology and Therapeutics:** Alprostadil (prostaglandin E<sub>1</sub>) produces vasodilation, inhibits platelet aggregation and stimulates intestinal and uterine smooth muscle. Smooth muscle of the ductus arteriosus, especially sensitive to alprostadil, relaxes in the presence of the drug. These effects are beneficial in infants who have congenital defects which restrict the pulmonary or systemic blood flow and who depend on a patent ductus arteriosus for adequate blood oxygenation and lower body perfusion. For this indication the drug is administered by continuous IV infusion into a large vein or through an umbilical artery catheter placed at the ductal opening

Alprostadil is useful for erectile dysfunction because it induces erection by relaxation of trabecular smooth muscle and by dilation of cavernosal arteries. This leads to expansion of lacunar spaces and entrapment of blood by compressing the venules against the tunica albuginea, a process referred to as the corporal veno-occlusive mechanism. For the treatment of erectile dysfunction, alprostadil is administered by injection into the corpora cavernosa or inserted intraurethraly

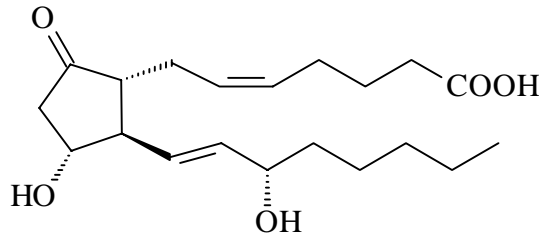
**Pharmacokinetics:** Systemically absorbed alprostadil is rapidly metabolized and inactivated. As much as 80% of the drug may be metabolized in one pass through the lungs, primarily by oxidation as described earlier for prostaglandins. Metabolites are excreted primarily by the kidneys, and excretion is essentially complete within 24 hours. No unchanged alprostadil has been found in the urine, and there is no evidence of tissue retention.

#### Adverse Reactions:

- ◆ Cardiovascular: Flushing, bradycardia, hypotension, tachycardia, edema and less commonly more severe effects such as cardiac arrest, congestive heart failure, second degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia and ventricular fibrillation.
- ◆ CNS: Fever, seizures, cerebral bleeding, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy and stiffness .
- ◆ GI: Diarrhea, gastric regurgitation and hyperbilirubinemia.

- ◆ Hematologic: Disseminated intravascular coagulation, anemia, bleeding, thrombocytopenia
- ◆ Renal: Anuria and hematuria
- ◆ Respiratory: Apnea, bradypnea, bronchial wheezing, hypercapnia, respiratory depression, respiratory distress and tachypnea

## II. Prostaglandin E<sub>2</sub> (Dinoprostone)



**Dinoprostone (PGE<sub>2</sub>)**

**Pharmacology and Therapeutics:** In pregnancy, PGE<sub>2</sub> is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labor. It is known that PGE<sub>2</sub> stimulates the production of PGF<sub>2</sub> $\alpha$  which in turn sensitizes the myometrium to endogenous or exogenously administered oxytocin. Although PGE<sub>2</sub> is capable of initiating uterine contractions and may interact with oxytocin to increase uterine contractility, available evidence indicates that, in the concentrations found during the early part of labor, PGE<sub>2</sub> plays an important role in cervical ripening without affecting uterine contractions. *This distinction serves as the basis for considering cervical ripening and induction of labor, usually by the use of oxytocin, as two separate processes.*

Failure of the cervix to undergo these natural physiologic changes prior to the onset of effective uterine contractions results in an unfavorable outcome for successful vaginal delivery and may result in fetal compromise. It is estimated that in » 5% of pregnancies the cervix does not ripen normally. In an additional 10% to 11%, labor must be induced for medical or obstetric reasons prior to the time of cervical ripening.

Based on their ability to stimulate the myometrium of the gravid uterus to contract in a manner similar to that seen in the term uterus these PG drugs are used for 1). initiation or continuation of cervical ripening in pregnant women at or near term with a medical or obstetrical need for labor induction (cervical ripening), 2). the management of missed abortion or intrauterine fetal death up to 28 weeks gestational age and, 3). management of nonmetastatic gestational trophoblastic disease (benign hydatidiform mole). Postpartum, the resultant myometrial contractions provide hemostasis at the site of placentation.

**Pharmacokinetics:** Dinoprostone gel and vaginal insert provide sufficient quantities of PGE<sub>2</sub> to the express therapeutic activity. PGE<sub>2</sub> is relatively rapidly absorbed (30 minutes). Systemically absorbed PGE<sub>2</sub> is completely metabolized in the lungs (first pass through pulmonary circulation), and the resulting metabolites are further metabolized in the liver and kidney. The pathways of metabolism include the oxidative processes described earlier. The major route of elimination of the products of PGE<sub>2</sub> metabolism is the kidneys. Half-life is estimated to be 2.5 to 5 minutes.

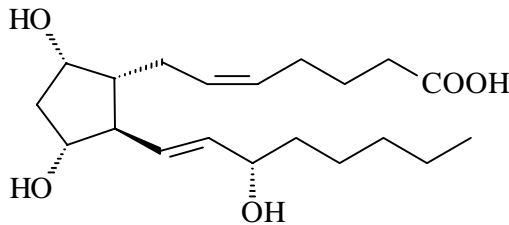
**Adverse Reactions:** The most frequent adverse reaction observed with dinoprostone as an abortifacient is nausea and vomiting which occur in about 66% of patients. Other

adverse effects include diarrhea, skin discoloration, unpleasant taste, dyspnea, and hyperpyrexia. Prostaglandins stimulate the smooth muscle of the GI tract and this activity may be responsible for the vomiting or diarrhea that may occur with their use. Body temperature elevation may also occur with PGE derivatives. Large doses of dinoprostone may lower blood pressure, probably as a result of its effect on smooth muscle of the vascular system. Large doses of dinoprostone can also elevate body temperature.

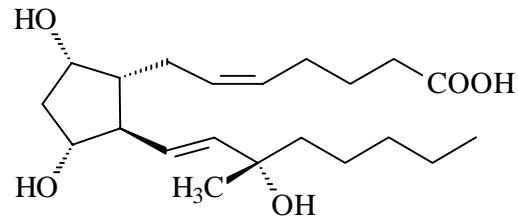
**Drug Interactions:** The activity of oxytocic agents (ergonovine, methylergonovine, oxytocin) may be augmented by the prostaglandins and thus concomitant use is not recommended.

### III. Prostaglandin F<sub>2α</sub> Derivatives

**Structure and Chemistry:** Carboprost is the 15-methyl analogue of PGF<sub>2α</sub> (dinoprost) and thus it is resistant to metabolic inactivation by oxidation at the 15-position. Thus carboprost has a longer duration of activity than dinoprost. Dinoprost was withdrawn in the US in the 1980s for financial reasons.



Dinoprost (PGF<sub>2α</sub>)



Carboprost (15-(S)-Methyl-PGF<sub>2α</sub>)

**Pharmacology and Therapeutics:** Carboprost has pharmacological properties similar to the PGE<sub>2</sub> derivative dinoprostone. It is used for second trimester abortion characterized by failure of expulsion of the fetus during the course of treatment by another method; premature rupture of membranes in intrauterine methods with loss of drug and insufficient or absent uterine activity; requirement of a repeat intrauterine instillation of drug for expulsion of the fetus; inadvertent or spontaneous rupture of membranes in the presence of a previable fetus and absence of adequate activity for expulsion; postpartum hemorrhage due to uterine atony that has not responded to conventional management (prior treatment should include use of IV oxytocin, etc.)

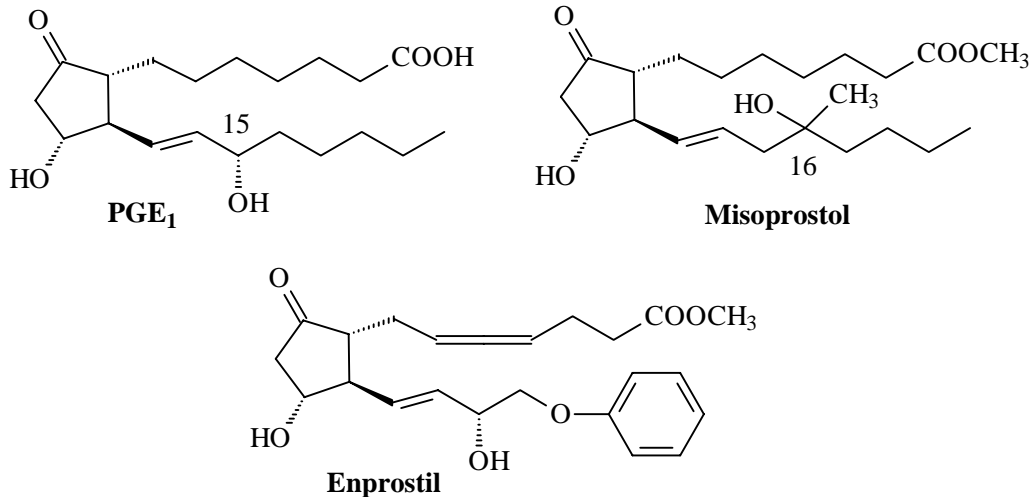
**Pharmacokinetics:** IM injection of carboprost yields peak plasma concentrations at 15 minutes. Six metabolites have been identified as a result of hepatic prostaglandin metabolism by the pathways described earlier. Less than 1% of the drug is excreted unchanged in the urine. Urinary excretion of metabolites is rapid and nearly complete within 24 hours following IM administration. About 80% of the dose is excreted in the first 5 to 10 hours and an additional 5% in the next 20 hours.

**Adverse Reactions:** The most common adverse effects are vomiting and diarrhea. Other adverse effects include leukocytosis, headache, fever, uterine rupture, bronchoconstriction, and flushing of the skin. Large doses of carboprost can elevate blood pressure, probably by contracting the vascular smooth muscle, but this has not been clinically significant with doses used for terminating pregnancy.

**Drug Interactions:** The activity of oxytocic agents may be augmented by the prostaglandins and thus concomitant use is not recommended.

### Prostaglandin E Derivatives for GI Disorders: Misoprostol (Cytotec™)

**Structure and Chemistry:** Misoprostol is a methyl ester derivative of PGE<sub>1</sub> in which the side chain hydroxyl group has been moved to position 16 and a methyl group added to protect it from metabolic attack and inactivation (oxidation). This drug is marketed as a the 16-R/S racemate and stereochemistry does not impact on activity. The ester is rapidly converted to the corresponding acid (16-methyl PGE<sub>1</sub>) by tissue and plasma esterases. Enprostil is another PGE<sub>1</sub> derivative marketed in foreign countries for treatment of ulcers. Enprostil contains a unique cummulative diene in the acid side chain and an oxyaryl substituent in place of the terminal four carbons octenol side chain. This type of functionality is also present in PG ocular hypotensive drugs.

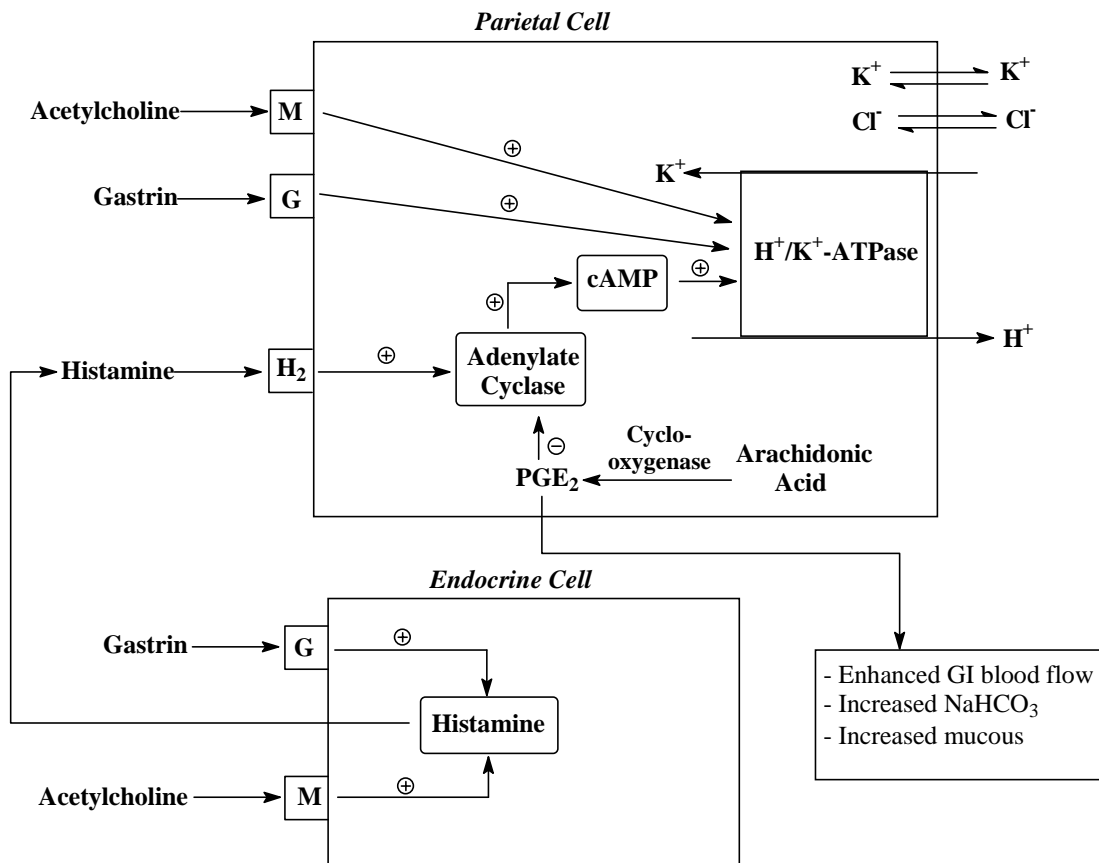


**Mechanism of Action:** A synthetic prostaglandin E1 analog with antisecretory (inhibiting gastric acid secretion) and cytoprotective activities. These activities are expressed through reversible and stereospecific binding to EP<sub>3</sub> receptors. These receptors have high affinity (K<sub>i</sub> 319 nM) for the acid metabolite of misoprostol and for other E type prostaglandins, but not for other sprostaglandin structural families or other GI-active agents (histamine, cimetidine, etc.).

- Antisecretory Actions: Misoprostol over the range of 50 to 200 mcg inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.
- Cytoprotective Activities: increased gastric blood flow, increased mucous and bicarbonate protection
- Immunologic Actions: One study demonstrated that misoprostol can inhibit basophil histamine release, thus it has a potential role as immunotherapy designed to reduce early-phase and late-phase allergic inflammation
- Reproductive Effects: Misoprostol produces uterine contractions that may endanger pregnancy (see Indications and Warnings below):

**Indications and Warnings:** To reduce the risk of NSAID-(including aspirin) induced gastric ulcers in patients at high risk of complications from a gastric ulcer (eg, the elderly and patients with concomitant debilitating disease), as well as patients at high risk of developing gastric ulceration (patients with a history of ulcer). Take misoprostol for the duration of NSAID therapy. Intravaginal and oral misoprostol has also been effective for termination of early pregnancy, especially in combination with mifepristone. In addition, misoprostol may be useful for induction of cervical ripening and labor, postpartum hemorrhage and preventing graft rejection .

This drug should be avoided in pregnancy and used with great caution in women of child-bearing age since it can cause abortion, premature birth, birth defects, etc. Also caution in patients with cerebral vascular or coronary artery disease (hypotensive effects) and uncontrolled epilepsy.



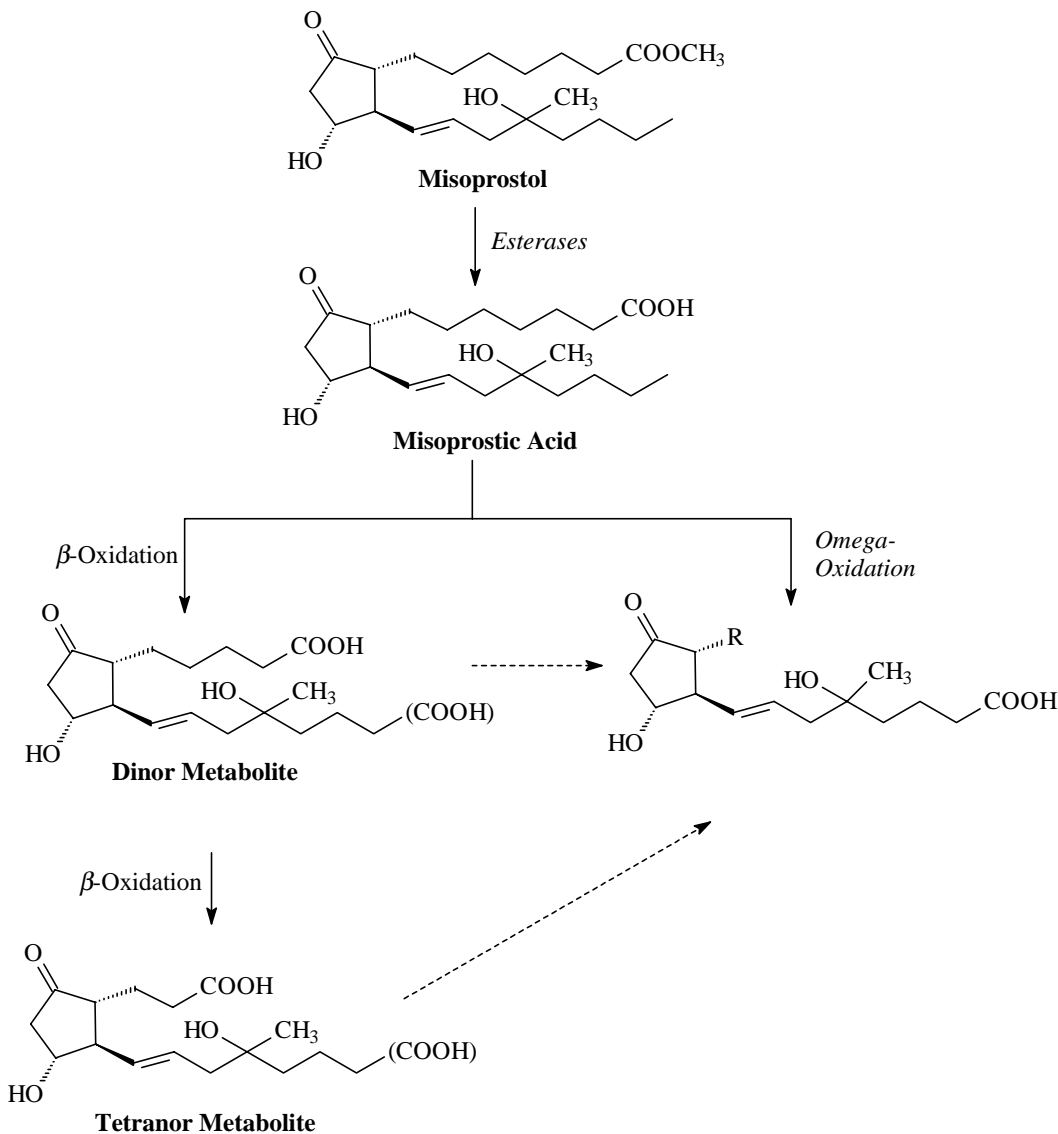
**Summary of Misoprostol (PGE<sub>1</sub>) mechanism of antisecretory and cytoprotective action**

**Pharmacokinetics:**

- Dosage for NSAID-Induced Ulcers: 200 micrograms 4 times daily with food for the length of NSAID therapy (100 and 200 mcg tablets). Multiple daily dosing is required

due to rapid clearance and reversible mechanism of this drug. See notes at end of section for dosing in other indications.

- Absorption and Onset: Misoprostol is extensively and rapidly absorbed (peak concentrations within 30 min) and undergoes rapid de-esterification to its free acid, which is responsible for clinical activity. Maximal antisecretory effects are observed within 2-3 hours and may persist for up to 4 hrs.
- Clearance: The active drug (misoprostic acid) is rapidly cleared with a terminal half-life of 20 to 40 minutes. Rapid metabolic inactivation by beta-oxidation and omega oxidation (liver and other tissues - See Figure). Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P450) enzyme system
- PPB: Misoprostol acid is about 80-90% and is concentration-independent in the therapeutic range.
- Elimination: About 80% elimination in the urine as metabolites (15% feces).
- Renal impairment: may increase half-life, maximum concentration, and area under the curve (AUC), but no clear correlation between degree of impairment and AUC. No routine dosage adjustment is recommended, but dosage may need to be reduced if usual dose is not tolerated.





Drug Interactions.

- Antacids reduce absorption, but minimal effect on kinetics. Reportedly a higher incidence of GI adverse reactions when taken with antacids.

Adverse Reactions:

- GI: Diarrhea (**risk of dehydration!**), abdominal pain, nausea, flatulence, dyspepsia, vomiting, and constipation. These actions appear to be mediated by EP<sub>1</sub> receptors.
- GU: Spotting, cramps, hypermenorrhea, menstrual disorder, dysmenorrhea, Postmenopausal vaginal bleeding may be related to misoprostol administration; workup to rule out gynecological pathology. Uterine contractility produced by misoprostol may be mediated by EP<sub>3</sub> receptors!
- Headache (2.4%).
- Hematologic toxicity (anemia, thrombocytopenia, etc.): Rare
- Cardiovascular adverse effects include chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmias, phlebitis, increased cardiac enzymes and syncope:  
Relatively rare

Misoprostol Dosing based on Indication/Use:

- NSAID-Induced Ulcers: 200 micrograms 4 times daily with food for the length of NSAID therapy (100 and 200 mcg tablets)
- Duodenal Ulcers: 800 micrograms/day in 2 or 4 divided doses for 4 weeks
- Abortion: Oral: mifepristone 600 milligrams as a single oral dose, followed in 2 days by Misoprostol 400 micrograms unless a complete abortion has been confirmed before that time. Intravaginal: 800 micrograms
- Cervical ripening and Labor: 50 micrograms repeated every 4 hours for two doses then 100 micrograms every 4 hours until membrane rupture. Intravaginal 25 micrograms every 3 to 4 hours
- Postpartum Hemorrhage: 600 micrograms given immediately after cord clamping .  
Rectal: 400 micrograms once
- Graft Rejection: 200 micrograms misoprostol added to standard immunosuppression with cyclosporine and prednisone

## Prostaglandin F<sub>2</sub> Derivatives for Glaucoma

### Introduction:

The primary therapeutic goal of glaucoma treatment is to lower intraocular pressure (IOP), the major risk factor for this disease. Clinical trials have shown that lowering IOP can slow disease progression, even in patients with intraocular pressure that is statistically “normal” (so called normal tension glaucoma). Pharmacologically, IOP can be reduced either by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow through the trabecular meshwork, through the uveoscleral pathway, or through a surgically created pathway.

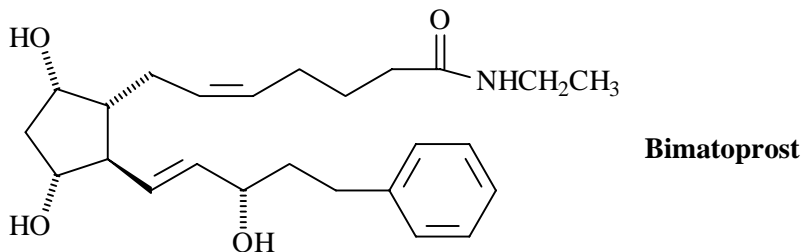
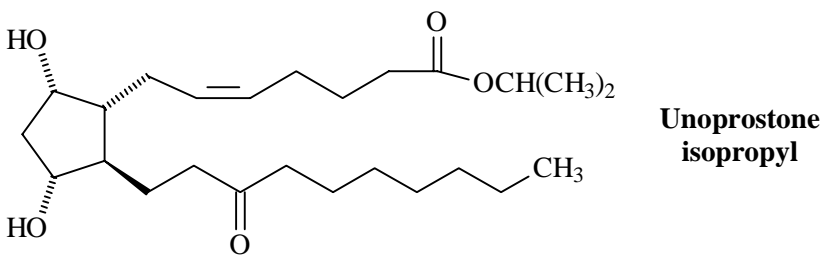
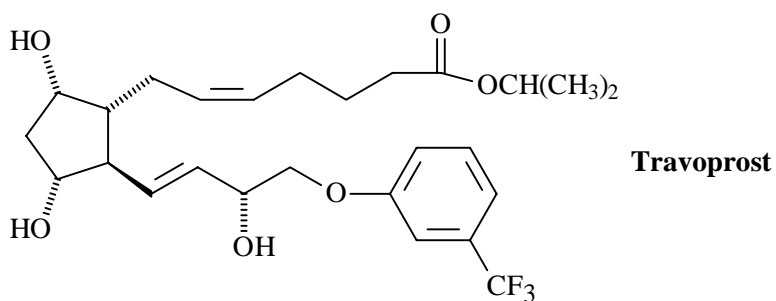
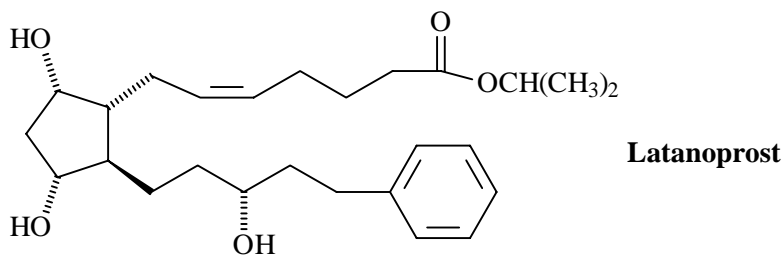
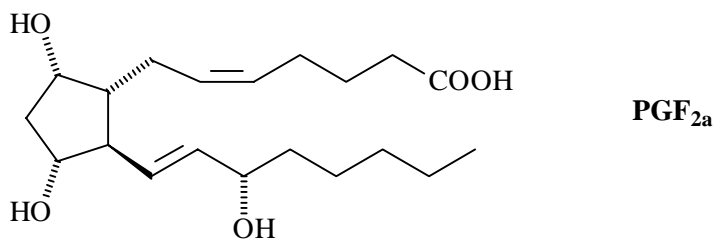
Pharmacotherapy employed for the long-term management of glaucoma falls into five classes:  $\alpha_1$ -adrenergic antagonists,  $\alpha_2$ -adrenergic agonists,  $\beta$ -adrenergic antagonists, carbonic anhydrase inhibitors, direct- and indirect-acting cholinergic agonists and, the newest class, prostaglandin (PGs) analogues. Topical beta-blockers have become first-line therapy of glaucoma because of their excellent pressure-lowering efficacy, long duration of action, and favorable ocular side effect profiles. However, cardiovascular and respiratory actions related to the systemic pharmacological actions of the beta-blockers may be particularly significant in elderly patients.

Intolerance to or a lack of adequate IOP-lowering efficacy of first-line therapy usually requires the addition of a second agent to the therapeutic regimen. In recent years the ocular hypotensive PGs have met this need because of advantages related to their mechanism of action and to their local and systemic pharmacokinetic profiles. Research in the 1970s indicated that simple ester derivative agonists of PGF<sub>2</sub> receptors (FP) elicited IOP reductions in rabbit eyes when administered in relatively low concentrations. However, the therapeutic potential of these early PGs was compromised by rapid development of tachyphylaxis as well as ocular hyperemic and other irritative effects. Researchers then initiated a drug discovery program that eventually led to the development and marketing of a series of prostaglandin glaucoma products including initially, latanoprost (*Xalatan*) and, most recently, travoprost (*Travatan*), bimatoprost (*Lumigan*) and unoprostone isopropyl (*Rescula*). The mechanism of IOP reduction by FP receptor agonists involves increased uveoscleral outflow. The ester PG ocular hypotensives are metabolically labile substances requiring bioactivation (in the cornea of the eye) after topical administration. Similarly, the bioactive PG species are readily bioinactivated should they achieve systemic distribution following ocular administration.

### Structure and Chemistry:

The PG ocular hypotensives are PGF<sub>2</sub> derivatives in which the heptenoic acid has been converted to either an ester or amide functionality. The esters are more lipophilic than the corresponding acid and penetrate ocular tissues more readily. Once inside, they are hydrolyzed to the acids (see below). All of these derivatives except unoprostone have an aromatic ring substituted in the octenoic acid side chain. This substitution does not effect FP receptor affinity or activity, but protects this group from omega-oxidation.

Unoprostone has a longer side chain and ketone group which is more lipophilic and resistant to metabolism. The PG ocular hypotensives are more selective for FP receptors than then endogenous PG.



### **Therapeutics:**

Ophthalmic solutions of these prostaglandin derivatives are approved as second-line agents for the reduction of intraocular pressure in patients who are intolerant of other intraocular lowering medications, or in patients who have had insufficient responses to other intraocular pressure lowering medications. These drugs are efficacious in lowering IOP in patients with open angle glaucoma or ocular hypertension and offer particularly ocular hypotensive activity in black patients. Generally, the IOP-lowering effect is in the 4-10 mmHg range. A number of these drugs were shown to be as effective or more effective than timolol. These drugs are devoid of systemic effects on pulse and blood pressure or pulmonary function. **It is important to note that, regardless of the claimed superiority of the PG ocular hypotensives to timolol, the latter drug remains as a first-line therapy while the PGs remain as alternative therapy.** The beta-blocker and PG drug classes have very different adverse effects, warnings and contraindications.

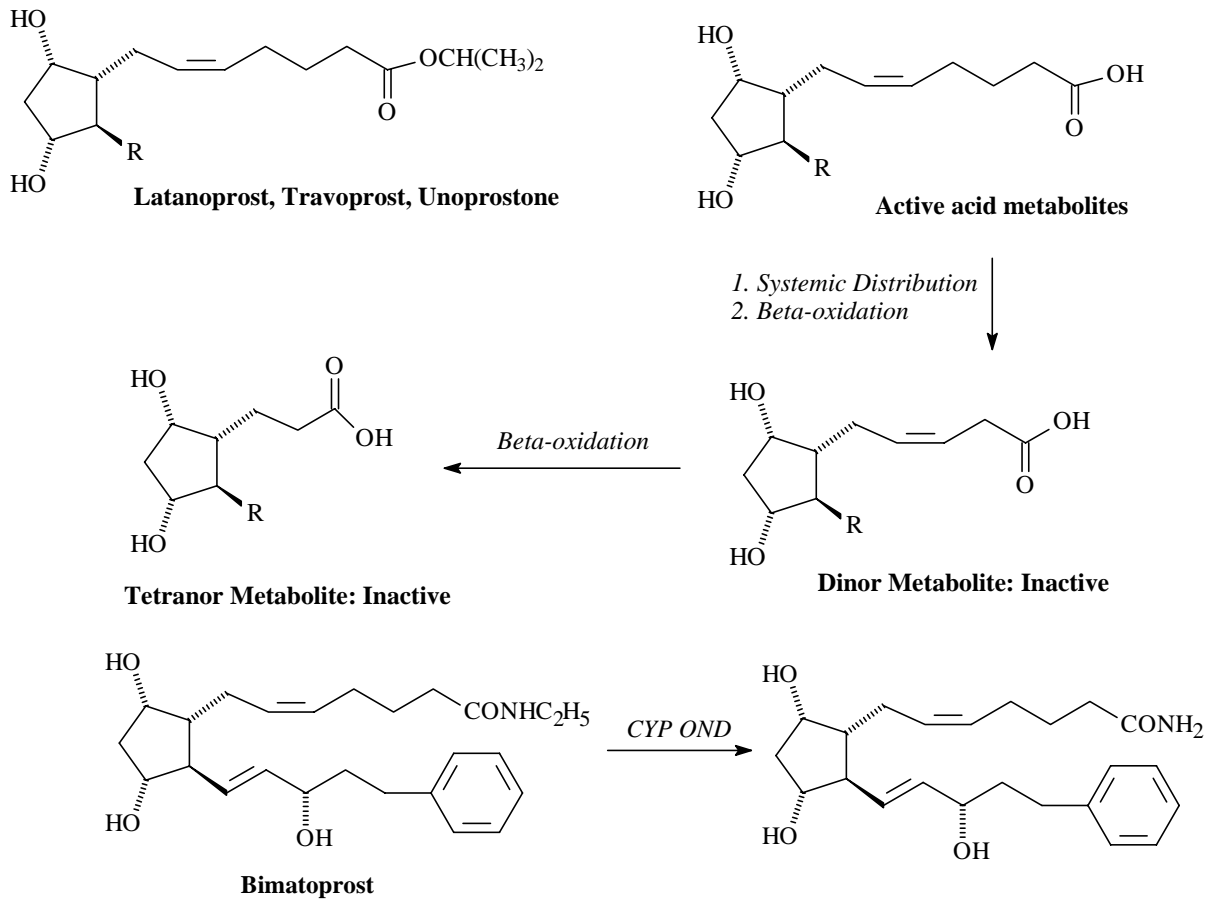
### **Adverse Reactions:**

- Ocular hyperemia and other irritative effects (burning/stinging, dry eyes, itching) are the most frequent events reported with the use of the ocular PGs. Melanogenic effects on the iris (increased iridial pigmentation) and hypertrichotic effects on eyelashes (increased growth) also may occur. These actions are apparently related to agonistic activity at FP and possibly EP receptors. The effect of these drugs on eye color may be related to an increase in the number of melanosomes in melanocytes. The long-term consequences of the melanogenic effect is currently unknown. Patients who are expected to receive PG treatment in only one eye should be advised of the potential for a disparity between the eyes with respect to eye color and eyelash length, thickness and/or number of eyelashes. **It should be noted that the synthetic PG hypotensives are less likely to cause a wide range of ocular side effects than endogenous PGF<sub>2</sub> due to their enhanced receptor selectivity.**
- A significant number of patients taking ocular PGs experience a flu syndrome and/or some other upper respiratory tract infection (pharyngitis, rhinitis, and sinusitis).

**Drug Interactions:** The PG ocular hypotensives may be used concomitantly with other topical ophthalmic drugs to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

**Pharmacokinetics:** Relatively little pharmacokinetic data are available describing the ocular disposition of these new PG analogues. After application to the eye, these drugs are absorbed through the cornea and conjunctival epithelium. While the active acid of the ester ocular PGs has been observed in ocular tissue, similar conversion of the amide (bimatoprost) to its acid has not been observed (and would be more difficult). In general, the PG agents display little systemic distribution (only nanogram/mL plasma levels 1 to 2 weeks dosing are observed). Drugs absorbed from the site of administration are moderately distributed in the body and metabolized rapidly via oxidative and conjugative pathways. Excretion of the systemically absorbed drugs and their metabolites is predominantly in the urine.

Systemically absorbed bimatoprost is metabolized by oxidative N-deethylation and other oxidative and glucuronidation pathways:



**Dosage & Administration:**

- Drug Products:

- Latanoprost: 0.004% ophthalmic solution
- Bimatoprost: 0.03% ophthalmic solution (pH 6.8-7.8)
- Travoprost: 0.004% ophthalmic solution (pH ~6)
- Unoprostone isopropyl: 0.15% ophthalmic solution

- Administration: One drop in the affected eye(s) once daily in the evening. Administration of these drugs more frequently than once daily is not recommended because the IOP-lowering effect of the PGs may be diminished. These drugs may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If two drugs are used, they should be administered at least five minutes apart.

**Prostaglandins for Treatment of Pulmonary Hypertension: Epoprostenol (Flolan™), Treprostinil (Remodulin™) and Beraprost (Procyclin™)**

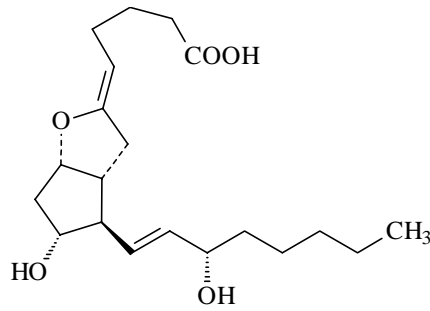
**Introduction and Pharmacology:**

Pulmonary arterial hypertension (PAH) is defined as abnormally high blood pressure in the arteries between the heart and lungs. PAH is classified as primary or secondary, depending on the origin of the pathology. Secondary PAH results from heart disease (congenital heart defects, left heart failure), lung disease (severe sleep apnea, emphysema, pulmonary emboli) liver disease, systemic connective tissue disease (such as scleroderma) or HIV infection. Primary PAH results directly from a disorder of lung blood vessels, a pathology commonly linked to the use of fenfluramine appetite suppressants (i.e. Fen-Phen). The results of a study published recently concluded that of 579 patients diagnosed with PAH at 12 medical centers in the US as many as 205 people with the primary form of the disease may have been affected by diet drugs. Fen-phen was pulled from the market in 1997 after it was discovered that it was the cause serious heart valve problems in many patients. It is estimated that approximately 100,000 people in the U.S. and Europe are afflicted with either primary or secondary PAH.

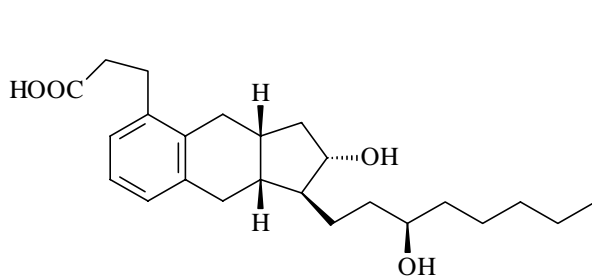
PAH affects more women than men and appears have a genetic basis with 6-10% of cases occurring in consecutive family generations. A specific chromosome that is related to PAH has been identified, but the exact nature of the defect remains to be determined. PAH causes a weakening of the lining of the lung's blood vessels resulting in leakage of blood which the muscles that surround the blood vessels to constrict. The continuous constriction increases the pressure within the blood vessels resulting in a choking off the flow of blood between the heart and lungs. The cutoff of blood damages the heart's right ventricle resulting in changes in shape and size, leading to heart failure and ultimately death. The first signs of the disease, such as mild shortness of breath, fatigue and difficulty exercising, are so subtle that the disease is often either misdiagnosed or not diagnosed until the patient's condition is far advanced. The survival rate for PAH in untreated patients is only 40 to 55 percent at two years from the onset of symptoms.

Presently, there is no cure for primary PAH, but there are several treatments that relieve the symptoms and thereby raise quality of life and increase life expectancy by several years. Current therapies include 1). calcium channel blockers (i.e. nifedipine) to improve the heart's ability to pump blood and lower pressure, 2). anticoagulants (i.e. Coumadin) to decrease the tendency of the blood to clot and permit blood to flow more freely, and 3). diuretics to decrease the amount of fluid in the body and reduce the work load on the heart. Once patients reach more advanced stages of PAH (WHO Class III and IV), drug therapy options are limited to the prostacyclin poprostenol (Flolan) and synthetic prostacyclin analogues.

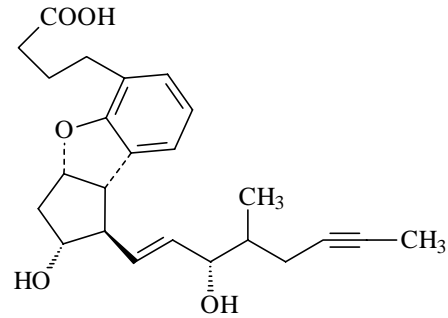
**Structure and Chemistry:** Eoprostenol is a derivative of naturally occurring PGI<sub>2</sub> and thus is too unstable for oral administration and is rapidly metabolized (to other PGs). Treprostinil and beraprost are stable synthetic prostacyclinomimetic drugs that are substantially more stable chemically and metabolically.



**Epoprostenol (Flolan™)**



**Treprostinil Sodium (Remodulin™)**



**Beraprost (Procyclin™)**

### **Pharmacology and Therapeutics:**

The prostacyclin drugs mimic the natural prostacyclin which causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, these drugs reduce right and left ventricular afterload, increase cardiac output and stroke, and promote removal of lipid deposits in vessels. These drugs have been shown to reduce dyspnea, fatigue and signs and other symptoms of pulmonary hypertension. Chronic therapy may also result in small positive changes cardiac index, mean pulmonary arterial pressure, pulmonary vascular resistance index, mean right atrial pressure, mean systemic arterial pressure, systemic vascular resistance index, mixed venous oxygen saturation and heart rate. These hemodynamic changes are consistent with drug-induced pulmonary and systemic vasodilation. These drugs have been credited with raising the life expectancy of patients with PAH by 3 to 5 years or more.

Unfortunately because of its short half-life (2-3 minutes) epoprostenol must be administered by continuously by intravenous infusion via a portable, battery-operated pump connected to a surgically implanted catheter placed in a vein in the neck or chest. Thus this therapy is very expensive (approximately \$100,000/year) and administration and maintenance of the pump and catheter line is complex. Treprostinil is a synthetic and stable form of prostacyclin derivative that can be administered by subcutaneous infusion. It has a longer half-life (4-6 hours) and thus can be administered subcutaneous infusion via a pager-sized MiniMed microinfusion device. This drug product also lowers the risk of sepsis infection and related hospitalization associated with

the epoprostenol catheter line. Beraprost differs from other members of this class in that it can be administered orally which may improve safety and compliance.

**Pharmacokinetics:**

- ◆ Because of its metabolic instability, epoprostenol must be administered by continuous IV infusion. It is rapidly like endogenous PGI<sub>2</sub> to other prostaglandins which are not effective for PAH. Its duration is only 5 minutes post-infusion. Epoprostenol is eliminated renally as PG metabolites and has an elimination half-life of less than 5 minutes (metabolism)
  
- ◆ Treprostinil is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. The recommended initial infusion rate is 1.25 ng/kg/min. The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive adverse effects of treprostinil (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction). Treprostinil is relatively rapidly and completely absorbed after subcutaneous infusion with an absolute bioavailability approximating 100%. Steady-state concentrations occur in about 10 hours. The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight and the drug is 91% bound to human plasma protein. Treprostinil undergoes substantial hepatic metabolism to yield five principle metabolites designated as HU1 through HU5. Metabolite HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). The chemical structure of HU1 is unknown. The enzymes of metabolism have not yet been identified and the pharmacologic activity and metabolic fate of these metabolites are not presently known. Based on the results of in vitro human hepatic cytochrome P450 studies, treprostinil does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether treprostinil induces these enzymes has not been studied. The elimination of treprostinil is biphasic, with a terminal half-life of approximately 2-4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Clearance in patients with hepatic insufficiency is reduced by up to 80% compared to healthy adults. Thus the initial dose of treprostinil should be decreased to 0.625 ng/kg/min ideal body weight in patients with mild or moderate hepatic insufficiency and should be increased cautiously. Treprostinil has not been studied in patients with severe hepatic insufficiency. No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given.



- ◆ Beraprost is orally effective and has an onset of action of 15-30 minutes and produces peak plasma levels in about 1.5 hours. It has an elimination half-life of 1 hour. Little else is known about the kinetics of this drug.
- ◆ Abrupt cessation of PG PAH therapy should be avoided since sudden large reductions in dose of treprostinil may result in worsening of PAH symptoms.

### **Adverse Reactions and Warnings:**

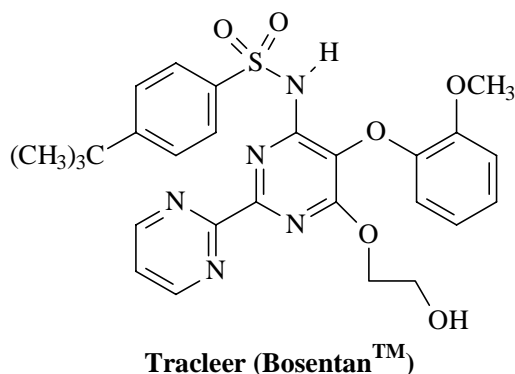
In clinical trials, patients receiving treprostinil reported a wide range of adverse events, most related to the route of drug administration and others possibly related to the underlying disease. Infusion site pain (85%) and infusion site reaction (83%) were the most commonly reported adverse events. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment. Other adverse events for these PG drugs in general include include headache, diarrhea, nausea, rash, jaw pain, vasodilatation, edema, dizziness, pruritus and hypotension. In clinical trials approximately 28% of patients reported problems with the treprostinil infusion system but most of these were readily managed or corrected by (e.g., replace syringe or battery, reprogram pump, straighten crimped infusion line). There were no reports of infection related to the drug delivery system.

**Drug Interactions:** During clinical trials, treprostinil was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. However, it should be noted that the reduction in blood pressure caused by treprostinil can be exacerbated by concurrent use of other antihypertensive drugs (diuretics, antihypertensive agents, or vasodilators). Also since treprostinil inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. This drug does not, however, affect the pharmacokinetics or pharmacodynamics of warfarin. Treprostinil has not been studied in conjunction with other drugs used to treat PAH including epoprostenol or bosentan. Treprostinil does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether treprostinil induces these enzymes has not been studied.

## Non-Prostaglandins for PAH: Bosentan (Tracleer™)

### Introduction and Pharmacology:

The observation that endothelin-1 levels are elevated in the plasma and lung tissue of patients with PAH suggested a pathogenic role for this neurohormone in the progression of PAH. Endothelin-1, via interaction with ETA and ETB receptors in the endothelium and vascular smooth muscle, produces blood vessel constriction and elevation of blood pressure. In addition to its vasomotor actions, endothelin-1 has been implicated in vascular remodeling in a number of animal models of restenosis. Bosentan was developed as a orally effective specific and competitive antagonist at endothelin receptors with higher affinity for ETA versus ETB receptors. By antagonizing the actions of endothelin-1 bosentan significantly reduces mean pulmonary artery pressure (MPAP), pulmonary vascular resistance (PVR), and mean arterial pressure (MAP).



**Therapeutics:** Bosentan is indicated to improve exercise ability and decrease the rate of clinical worsening of pulmonary arterial hypertension (PAH) in patients with WHO Class III or IV symptoms. This drug significantly improves exercise capacity in both primary and secondary PAH. Treatment with bosentan also is associated with a significant delay in the time to clinical worsening as defined as death, hospitalization, worsening PAH or initiation of intravenous therapy, as well as significant improvement in functional status, breathlessness and hemodynamics (blood circulation).

**Pharmacokinetics:** The absolute bioavailability of bosentan in healthy volunteers is approximately 50% and is unaffected by food. After oral administration, maximum plasma concentrations of bosentan are attained within 3 to 5 hours. The volume of distribution is about 18 L. and the drug is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes. Three bosentan metabolites have been detected, one of which is pharmacologically active and may contribute to some extent (10-20%) to the therapeutic effect of the parent drug. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Total clearance after a single IV dose is about 8 L/hr. Upon multiple dosing, plasma concentrations decrease gradually to 50% to 65% of those seen after single doses, probably as a result of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3 to 5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less

than 3% of an administered oral dose is recovered in urine. The terminal elimination half-life is approximately 5 hours. The pharmacokinetics of bosentan have not been determined in patients with PAH, but exposure is expected to be greater in such patients because increased (30% to 40%) bosentan exposure was observed in patients with severe chronic heart failure. The influence of liver impairment on the pharmacokinetics of bosentan has not been evaluated, but in vitro and in vivo evidence showing extensive hepatic metabolism of this drug suggests that liver impairment would significantly increase exposure of bosentan. Thus caution should be exercised when bosentan is used in patients with mildly impaired liver function, and the drug should be avoided in patients with moderate or severe liver abnormalities or elevated aminotransferases (see Dosage and Administration below). In patients with severe renal impairment (Ccr 15 to 30 mL/min), plasma concentrations of bosentan are essentially unchanged and while plasma concentrations of the three metabolites were increased nearly two-fold compared. These differences do not appear to be clinically important.

**Dosage and Administration:** Because of potential liver injury and in an effort to make the chance of fetal exposure to bosentan as small as possible, bosentan may be prescribed only through the bosentan Access Program. Bosentan tablets should be administered in the morning and evening, with or without food. Bosentan treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. In patients with a body weight < 40 kg but who are > 12 years of age, the recommended initial and maintenance dose is 62.5 mg twice daily. Doses greater than 125 mg twice daily do not appear to confer additional benefit sufficient to offset the increased risk of liver injury. If aminotransferase levels are confirmed to > 3 but ≤ 5 times the upper limit of normal (ULN), the daily dose should be reduced or treatment interrupted and aminotransferase levels monitored at least every 2 weeks. If the aminotransferase levels return to pretreatment values, treatment can be continued or reintroduced as described below. If aminotransferase levels are confirmed to >5 but ≤8 ULN drug therapy should be stopped and aminotransferase levels monitored at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, reintroduction of the treatment can be considered. If aminotransferase levels are confirmed to >8 ULN drug treatment should be stopped and not reintroduced since there is no experience with reintroduction of bosentan in these circumstances. If cases where bosentan is reintroduced, it should be at the starting dose and aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (eg, nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue) or increases in bilirubin ≥ 2 × ULN, treatment should be stopped. There is no experience with the reintroduction of bosentan in these circumstances. There is limited experience with abrupt discontinuation of bosentan but no evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

**Adverse Reactions and Warnings:** Bosentan is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Therefore, pregnancy must be excluded prior to initiation of

bosentan therapy, and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan. Monthly pregnancy tests should also be performed. Also, it is not known whether bosentan is excreted in breast milk and therefore taking this drug while breastfeeding is not recommended.

In clinical trials three-fold increases of liver aminotransferases (AST or ALT) were seen in 12% of PAH patients on 125 mg of bosentan twice daily and 14% of PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to  $\geq 3$  times the upper limit of normal (ULN) were associated with aminotransferase increases in 0.3% of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of  $>3 \times$  ULN) and increases in total bilirubin ( $\geq 3 \times$  ULN) is a marker for potential serious liver injury and thus serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. Elevations of AST or ALT can occur early and late in treatment, usually progress slowly and are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with bosentan. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated (see Dosage and Administration). Also bosentan therapy should be avoided in patients with moderate or severe liver impairment.

In patients with PAH treated with doses of 125 or 250 mg of bosentan twice daily marked decreases in hemoglobin occurred in 3% of treated patients (versus 1% in placebo-treated patients). A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared with 29% of placebo-treated patients. In 80% of these patients the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared with 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis. Hemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. If a marked decrease in hemoglobin concentration occurs, further evaluation is required to determine the cause and need for specific treatment.

**Drug Interactions:** Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes by other drugs may therefore increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these isoenzymes will be decreased when bosentan is coadministered. Bosentan has no significant inhibitory effect on any CYP isoenzymes tested (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) and thus it is not expected to increase the plasma concentrations of drugs metabolized by these enzymes. Bosentan is contraindicated for use with cyclosporine A and glyburide.