It is difficult for the average practitioner to find unbiased information about newly released drugs. We have decided to help to fill this void by picking high profile new drugs, compiling and assessing the available evidence, and identifying the initial role the drug should play in our therapeutic armamentarium.

**Losartan (Cozaar)**

**Indication:** Hypertension.

**Mechanism of Action:** Type 1 Angiotensin II receptor antagonist. Through this action losartan modulates the renin-angiotensin system at a site different from the angiotensin converting enzyme (ACE) inhibitors. The action of ACE inhibitors to decrease bradykinin breakdown is possibly involved in some of the beneficial and adverse effects of the drugs (see Fig.).

**Pharmacokinetics:** The major route of inactivation is liver metabolism. The elimination t½ of losartan averages 2 hours; the main metabolite is active and has an average t½ of 5 hours (Br J Clin Pharmacol, 35:290, 1993).

**Evidence of efficacy:** There are 4 published randomized controlled trials (RCTs) comparing the antihypertensive efficacy of losartan (10-150 mg once daily) with placebo (Arch Intern Med, 155:405, 1995), enalapril, 20 mg once daily, (Hypertension, 25:1345, 1995, Hypertension, 25:37, 1995) and atenolol, 50 mg once daily, (Amer J Hypertens, 8:578, 1995). These studies demonstrate that losartan lowers blood pressure more than placebo and similar to enalapril and atenolol. In these studies the maximal antihypertensive effect occurred with 50 mg losartan. There are no data to demonstrate effectiveness of losartan in congestive heart failure, post myocardial infarction or diabetic nephropathy.

**Adverse effects:** Other than a low incidence of dizziness, losartan was not associated with any adverse effects at a significantly higher rate than placebo. Dry cough does not appear to be a problem with angiotensin II antagonists, presumably because they do not have any effects on bradykinin metabolism (J Hypertens, 12:1387, 1994). As with ACE inhibitors, losartan is contraindicated during pregnancy.

**Dose and Cost:** Losartan is available in 25 ($1.10) and 50 ($1.10) mg unscored tablets, which can be halved. The average daily cost for 12.5 to 100 mg daily is $0.55-2.20. The daily cost range for the 9 ACE inhibitors available in B.C. is $0.45-2.10.

**Conclusions:** Losartan, starting with a dose of 12.5 mg once daily, may be considered in patients who require an ACE inhibitor (see Therapeutics Letter 8) but who cannot tolerate it due to drug-induced dry cough. At the present time it is not known whether angiotensin II receptor antagonists will improve survival in heart failure or after a myocardial infarction.

**Lansoprazole (Prevacid)**

**Indications:** Acute gastric and duodenal ulcer, severe erosive reflux esophagitis.

**Mechanism of Action:** Suppresses gastric acid secretion by inhibition of the proton pump.

**Pharmacokinetics:** The major route of inactivation is liver metabolism. After a 30 mg dose there
are marked inter-individual differences in plasma concentrations and t1/2, (range, 0.4-8.5 hours).

**Evidence of effectiveness:** Three published double-blind RCTs comparing omeprazole with lansoprazole were found: 8 week trial for acute gastric ulcer (Gastroenterology, 104:A80, 1993), 4 week trial for active duodenal ulcer (Scand J Gastroenterol, 30:210, 1995) and an 8 week trial for the treatment of reflux esophagitis (Scand J Gastroenterol, 28:224, 1993). These studies demonstrate that lansoprazole, 30 mg daily, is approximately equivalent to omeprazole, 20 mg daily, in healing rate and symptom relief.

**Adverse effects:** The most frequent adverse effects reported in short-term studies were diarrhea (3.3%), headache (1.5%), constipation (1.2%), asthenia (1.1%), dizziness (1.1%), and abdominal pain (1.0%). Concerns about long-term safety are the same as for omeprazole (see Therapeutics Letter 3).

**Dose and Cost:** Available in 15 mg ($2.00) and 30 mg ($2.20) capsules as compared with omeprazole 20 mg tablets (~$2.30).

**Conclusions:** Lansoprazole is a proton pump inhibitor which is similar to omeprazole in potency, pharmacokinetics, safety and effectiveness.

**Cefprozil (Cefzil)**

**Indications:** Bacterial pharyngitis/tonsillitis, otitis media, uncomplicated skin infections, uncomplicated urinary tract infections.

**Mechanism of action:** First generation cephalosporin. Inhibits bacterial cell wall synthesis like other cephalosporins. Similar antibacterial spectrum to cephalexin, cefaclor, cefuroxime axetil, cefixime and amoxicillin-clavulanate.

**Pharmacokinetics:** Excellent oral absorption with elimination by tubular secretion in the kidney. Average elimination t1/2 is 1.3 hours.

**Evidence of effectiveness:** There are at least 11 published RCTs comparing cefprozil with other antibiotics in the treatment of the infections listed above (Ann Pharmacother, 27:1082, 1993). In only one of these studies was cefprozil compared with the first line choice as defined by the Anti-Infective Guidelines for Community-acquired Infections (distributed to you with Letter 5). In these studies there were no proven advantages in clinical or bacteriologic response rate.

**Adverse effects:** The main adverse events in 4226 patients were diarrhea (3.0%), nausea (2.3%), and vomiting (1.4%). Rash occurred in 2.1% of children under 13 years of age. In the above studies amoxicillin/clavulanate had a higher incidence of diarrhea than cefprozil and cefprozil had a higher incidence of rash than erythromycin.

**Dose and Cost:** Available in 250 mg and 500 mg tablets and 125 mg/5ml and 250 mg/5ml suspension. Usual dose in adults is 250 mg BID ($3.06/day), and in children 15 mg/ kg q12h ($0.18/kg/day). See Anti-Infective Guidelines for comparative prices.

**Conclusions:** Cefprozil is a new oral cephalosporin, which should be reserved for patients who are allergic or intolerant to the first or second line choices.

**Zuclopenthixol (Clopixol)**

**Indications:** Manifestations of acute and chronic schizophrenia.

**Mechanism of action:** Zuclopenthixol is the neuroleptically active cis-stereoisomer of clopenthixol, which belongs to the thioxanthene group of neuroleptics, eg. flupenthixol. It is a high affinity antagonist for both dopamine D1 and D2 receptors, and is also a weak antagonist for noradrenaline, histamine and cholinergic receptors.

**Pharmacokinetics:** The major route of inactivation is liver metabolism; average elimination t1/2 is 20 hours.

**Evidence of effectiveness:** In 1978 zuclopenthixol was shown to be similar in effectiveness and twice as potent as clopenthixol. Since then at least five double-blind RCTs comparing zuclopenthixol with haloperidol in the treatment of acute and chronic schizophrenia have been published. These trials demonstrate that the drugs are similar in effectiveness and incidence of side effects (Curr Med Res Opin, 12:594, 1992)

**Adverse effects:** As with other neuroleptics the incidence of adverse effects is high; the four most common adverse effects are drowsiness (32%), extrapyramidal symptoms(19%), dry mouth(15%), fatigue(15%), and dizziness(11%).

**Dose and cost:** Available in tablets, injection and depot formulations. The usual oral maintenance dose range is 20-60 mg daily ($0.72-2.16), as compared to haloperidol, 2.5-10 mg daily ($0.10-0.29), flupenthixol, 3-9 mg daily ($0.56-1.68), loxapine, 25-100 mg daily ($0.61-1.60) and risperidone, 3-8 mg daily ($3.23-8.36).

**Conclusions:** Zuclopenthixol is a thioxanthene neuroleptic similar to flupenthixol. It has no distinctive advantages over haloperidol and other neuroleptics and should be reserved for selected patients who fail to respond or are intolerant to other neuroleptics.

Next Therapeutics Letter:

**Hormone Replacement Therapy**

Drugs to be covered in the next New Drugs Letter: torsemide, a loop diuretic, etodolac, a non-steroidal anti-inflammatory drug, famciclovir, an anti-viral drug, and naltrexone, a long acting opioid receptor antagonist.