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UK Drug Information Pharmacists Group

NEW MEDICINES ON THE MARKET

Evaluated Information for NHS Managers, Budget Holders and Prescribers.

IMIDAPRIL

Summary

- Imidapril is a new ACE inhibitor licensed for the treatment of essential hypertension.
- Clinical trials show that imidapril 5-10mg once daily is as effective as enalapril 5-10mg once daily and nifedipine SR 20-40mg twice daily in reducing blood pressure.
- Imidapril is well tolerated. Further evidence is required to confirm that the incidence of cough is less with imidapril than with enalapril.
- At standard doses only (5-10mg daily) imidapril is less expensive than other ACE inhibitors at equivalent doses.
- When non-drug treatment, a thiazide and/or a beta-blocker are ineffective or inappropriate for the treatment of patients with essential hypertension, imidapril provides an effective alternative to other ACE inhibitors, but offers no significant clinical advantage.

Date Published: August 1999 Monograph Number: 4/99/12 Marketed: May 1999

Region of Origin to whom queries should be directed: South and West (Southampton)

IMIDAPRIL

APPROVED NAME: Imidapril

BRAND NAME: Tanatril (Trinity Pharmaceuticals Ltd)

SYNONYM(S): SH 6366, TA 6366

PRESENTATION: 5mg and 10mg tablets

THERAPEUTIC CLASS: ACE Inhibitor (BNF 2.5.5.1)

LICENSED INDICATIONS: Treatment of essential hypertension

DOSE/ADMINISTRATION: 5mg once a day, increasing if necessary after 3 weeks of treatment to 10mg once daily. If blood pressure remains uncontrolled consider combination therapy with a diuretic, or increase dose to a maximum of 20mg daily.
Tablets should be taken at about the same time of day about 15 minutes before meals.
Elderly patients 2.5mg once a day titrated according to blood pressure to a maximum of 10mg a day.
Do not use in moderate to severe renal impairment. Reduce dose in mild renal impairment or hepatic impairment.

THERAPEUTIC COMMENT: Imidapril is a new ACE inhibitor as effective as enalapril for hypertension.

COST/COURSE (28 days): 5mg £5.92; 10mg £6.69; 20mg £13.38

TREATMENT ALTERNATIVES:

	Enalapril	5mg £7.86	10mg £11.03	20mg £13.10
	Lisinopril	5mg £9.58	10mg £11.83	20mg £13.38
	Ramipril	2.5mg £7.51	5mg £9.55	10mg £13.00
Also	Valsartan		80mg £15.75	160mg £19.69

28 days therapy (MIMS and Drug Tariff July 1999)

IMIDAPRIL

INTRODUCTION

Antihypertensive therapy has improved the outlook for patients with high blood pressure by decreasing the frequency of stroke, heart failure, and renal failure: treatment also reduces the incidence of coronary events. The Joint British Recommendations on prevention of coronary heart disease in clinical practice advise a target systolic blood pressure of less than 140mm Hg and diastolic blood pressure of less than 85mm Hg; the target in diabetes is lower [1].

The strategy for reducing blood pressure is probably best as follows:-[1]

1. Non drug treatment (obesity, high alcohol intake, high salt intake, lack of regular exercise, and smoking - these should be corrected).

2. Thiazide diuretic.

3. Beta blockers (used with thiazide where not effective alone).

4. a) ACE inhibitors.
   or
   b) Calcium channel blockers.

5. Other drugs - vasodilators, alpha-blockers, and centrally acting drugs.

ACE inhibitors are established treatment for hypertension (and heart failure). Clinically relevant differences are few and far between, particularly in the treatment of hypertension when the optimal dose and dose intervals are used [2].

PHARMACOLOGY

Imidapril is an angiotensin-converting enzyme (ACE) inhibitor (similar to enalapril, lisinopril, ramipril etc) which inhibits the conversion of angiotensin I to angiotensin II [1,3]. This leads to marked peripheral vasodilation and blood pressure lowering effects [3,4]. In a phase I study, imidapril caused a reduction in blood pressure from 6 hours after administration [5].

PHARMACOKINETICS

Following oral administration imidapril is about 70% absorbed and reaches its maximum plasma concentration within 2 hours. A fat-rich meal significantly reduces the absorption of imidapril [3]. Imidapril is mainly hydrolysed to the active metabolite, imidaprilat. Maximum plasma concentration of imidaprilat are achieved within 7 hours. Initial half-life is about 7-9 hours and the terminal half-life more than 24 hours [3].
Protein binding of imidapril and imidaprilat is 85% and 53% respectively. After oral administration of radio labelled imidapril, 40% of total radio activity is excreted in urine and about 50% in faeces [3].

Maximum ACE-inhibition is about 75% after a single dose and at steady state [6]. ACE inhibition before drug intake at day 28 (ie trough) was 50% [6]. Increased plasma levels and AUC values of imidapril and imidaprilat have been reported in patients with renal impairment. The increase in AUC of imidaprilat was two fold in patients with moderate renal impairment and nearly tenfold in severe renal impairment [3,7]. In patients with hepatic impairment the conversion of imidapril into imidaprilat was delayed, but there were no statistically significant differences in peak levels or AUC compared to patients with normal hepatic function [8].

EFFICACY

a) Dose finding studies

Patients with mild to moderate essential hypertension (mean sitting diastolic blood pressure 103.4mm Hg (sd 0.62) received placebo or imidapril 2.5mg, 5mg, 10mg or 20mg in a 2 week study (n=91), or imidapril 5mg, 10mg, 20mg or 40mg in the 4 week study (n=162). Compared with placebo, imidapril 10mg, 20mg and 40mg daily significantly reduced diastolic pressure, with no significant difference between the doses. The 2.5mg dose showed no significant effect, and the 5mg dose an intermediate effect [9]. In a similar study moderate to marked blood pressure reduction was achieved in 4/19 patients with imidapril 2.5mg/day, 9/19 with ≤ 5mg/day, and 12/19 ≤ 10mg/day [10].

b) In combination with thiazide diuretics

A multicentre open trial in 62 patients with mild to moderate hypertension showed that imidapril in combination with a fixed dose of a thiazide (not stated) was effective in reducing blood pressure to < 150/90mm Hg as follows: imidapril 2.5mg/day 13 patients, 5mg/day 21 patients, 10mg/day 11 patients, and 20mg/day 3 patients. 1 patient withdrew due to dizziness [11]. Combination therapy has also been studied long-term (see below).

c) Long-term treatment

In a long term extension study of 82 patients with mild to moderate hypertension treated with imidapril over one year, 49 patients (90.7%) on monotherapy and 20 (76.9%) on combined therapy maintained or improved the reduction in blood pressure to 150/90mm Hg [12].

d) Comparative studies

In a multicentre, randomised, double blind, parallel group study published only as an abstract, 161 patients with seated diastolic blood pressure of 95-115mm Hg were treated with placebo (n=55) or imidapril 5-20mg/day titrated at 2 week intervals for the first 4 weeks of the study if the blood pressure remained >90mm Hg. After 8 weeks 33% of patients on placebo and 49% patients on imidapril attained a diastolic blood pressure of ≤ 90mm Hg. 38% placebo patients and 61% imidapril patients were classified as responders ($p < 0.01$ vs placebo) [13].

A multicentre, randomised, double blind study was carried out in 231 outpatients with mild to moderate hypertension (systolic blood pressure ≥ 160mm Hg and diastolic blood pressure ≥ 95mm Hg). Patients received imidapril or enalapril 5mg once a day, increasing to 10mg in patients whose antihypertensive response was insufficient after 4 weeks. After 12 weeks the antihypertensive effect was considered sufficient when the blood pressure fell to ≤ 149/89mm Hg, or fell by ≥ 20/10mm Hg. An adequate response was observed in 71.3% (77/108) patients on imidapril and in 66.1% (76/115) on enalapril, with no significant difference between the groups. Imidapril showed antihypertensive activity comparable to that of enalapril [14].

In a further multicentre crossover trial imidapril 5-10mg/day was given to 246 patients and enalapril 5-10mg/day to 243 patients with mild to severe hypertension. After 12 weeks patients were switched to the other therapy for a further 12 weeks. No significant difference was observed in antihypertensive effect between imidapril and enalapril [15].

A double blind, randomised, parallel group study was carried out in 86 patients with hypertension (BP >140/95mm Hg). Patients were treated with nifedipine SR 20mg twice daily or imidapril 5mg once daily for 6 months. Doses were doubled if BP exceeded 140/90mm Hg. Nifedipine SR reduced BP from 144/93 to 132/85mm Hg and imidapril reduced BP from 147/95 to 135/86mm Hg at 6 months. Thus imidapril was as effective as nifedipine SR [16].

e) Heart Failure

244 patients with mild to moderate chronic heart failure stable on digoxin and diuretics were treated for 12 weeks with imidapril 2.5mg, 5mg, or 10mg. Exercise time increased in the 10mg group ($p=0.02$), but not in the 5mg or 2.5mg groups compared to placebo. Physical working capacity also increased in a dose related manner [17]. As yet, imidapril is not licensed for the treatment of heart failure in UK.

PROMOTIONAL DATA

The manufacturer claims powerful, affordable ACE inhibition, with proven clinical performance, excellent tolerability and cost effectiveness.

Clinical studies show that imidapril 5-10mg once daily is as effective as enalapril 5-10mg once daily and nifedipine SR 20-40mg twice daily.

Imidapril is well tolerated. The incidence of cough is less with imidapril than with enalapril in two clinical trials (see below). However, further evidence is required to confirm this. In the meantime the manufacturer is not claiming a lower incidence of cough with imidapril.

At standard doses only (5-10mg daily) imidapril is less expensive than other ACE inhibitors at equivalent doses.

ADVERSE EFFECTS

Refer to SPC for full details

The incidence of adverse events in hypertensive patients on imidapril was 34% with imidapril and 36% for placebo. Cough, dizziness, fatigue, somnolence, dyspepsia and vomiting occurred more frequently in the imidapril group [3].

In published studies cough has been reported to occur less frequently than with enalapril. Cough was reported in 0.9% (1/108) patients on imidapril 5-10mg/day, and in 7.0% (8/115) patients on enalapril 5-10mg/day. Other side effects were similar occurring in 4.6% patients on imidapril and 5.2% on enalapril [14]. A higher incidence of cough with both drugs was reported in another study of 496 patients with 15% (32/210) patients on imidapril and 39% (85/220) on enalapril. 21% of patients who did not experience cough while receiving imidapril, developed a cough after switching to enalapril. Conversely a cough developed in 0.9% patients who crossed over to imidapril [15,18].

Other adverse effects are similar to other ACE inhibitors - see SPC.

CONTRA-INDICATIONS/PRECAUTIONS:

Refer to SPC for full details

Contra-indications:
Hypersensitivity to imidapril or any other ACE inhibitor, history of angioneurotic oedema, hereditary/idiopathic angioedema, pregnancy, lactation, renovascular hypertension, renal failure (creatinine clearance < 10ml/min).

Precautions: as with other ACE inhibitors.
Kidney transplantation, psoriasis, hypotension, renal insufficiency, hypersensitivity to insect toxins/bites, hyperkalaemia, surgery/ anaesthesia, aortic stenosis/hypertrophic cardiomyopathy, neutropenia/agranulocytosis, proteinuria.
Drug interactions: digoxin [19], potassium sparing diuretics or potassium supplements, diuretics, lithium, anaesthetics, narcotic drugs and antipsychotics, antihypertensives, allopurinol, cytostatic or immunosuppressive agents, corticosteroids, procainamide, NSAIDs, rifampicin, antidiabetics, antacids, sympathomimetics, alcohol.

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