

CHAPTER THREE: THE COZAAR CHALLENGE

The focus of this chapter is on MSD's competitive position within the SA pharmaceutical industry. Particular attention is paid to the challenges and opportunities that lie ahead of COZAAR, MSD's largest product and primary driver of growth. The chapter also includes a summary of the COZAAR marketing strategy with reference also to the proposed role of e-Marketing.

3.1 MSD IN THE MARKET

According to IMS (TPM, June 2005), MSD is ranked 7th in the market in terms of annual revenue, with a market share of 3%. To put this in perspective, Synofi-Aventis is ranked 1st, with a market share of 7%. Up until September 2004, MSD had been growing relatively well. Figure 3.1 below, shows MSD sales for the last three years. However, in September 2004, MSD lost its largest product VIOXX, which was also the second largest product in the total SA market; and this had a huge impact on MSD. VIOXX was withdrawn from all international markets because of safety concerns relating to a new clinical study that showed that VIOXX may cause increased risk of cardiovascular events such as heart attacks and strokes during chronic use.

For MSD (SA) the loss of VIOXX meant the immediate loss of a projected R100 million in sales for 2005 alone. However, the bigger problem for MSD relates to the effect that the VIOXX withdrawal would have on both long range sales forecasts (and targets) and long range resource allocation plans. Consequently MSD's management have had to develop and implement strategies to redeploy unused sales force and marketing staff; and simultaneously increase sales amongst remaining product lines. Management has also had to focus on more innovative ways to reduce the overall cost of sales and marketing, and optimise ROI.

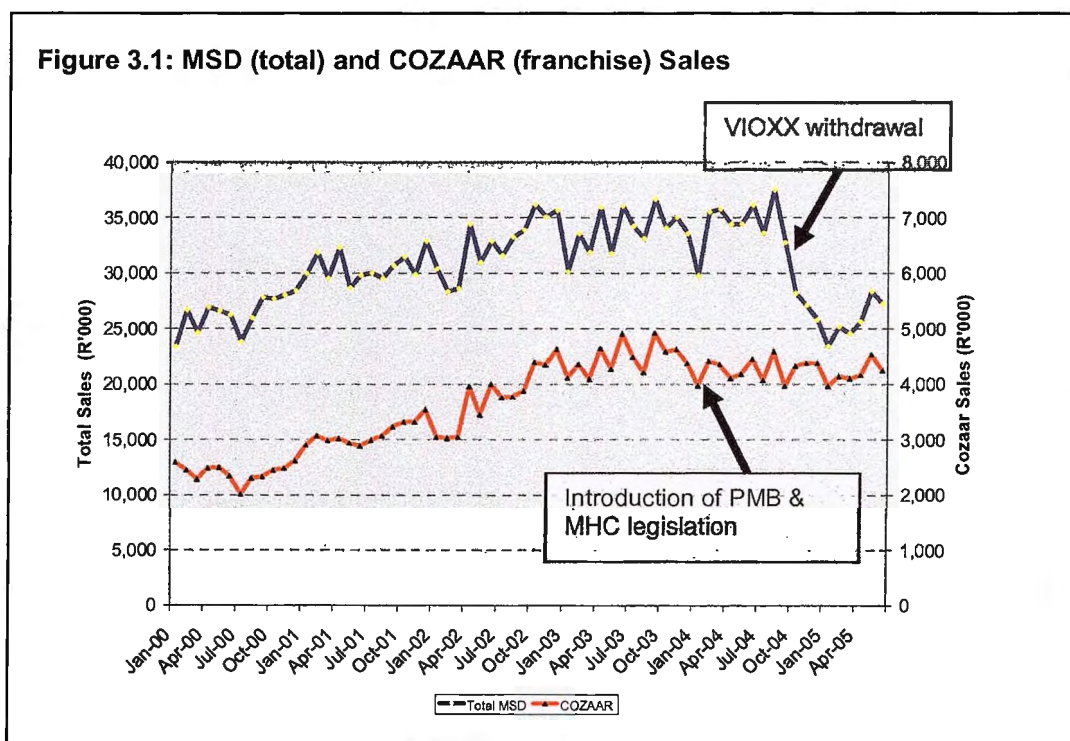
The COZAAR, SINGULAIR, FOSAMAX and EZETROL sales and marketing teams; that market the remaining MSD blockbusters, are now faced with the

challenge of having to deliver even greater growth over 2006/7 than was originally anticipated. Only in this way will MSD be able to deliver on their long range targets and avoid downsizing over the next 2 years. E-marketing is one of the possible vehicles for driving growth of these products and as a result, both SINGULAIR and COZAAR have already begun investing resources accordingly.

3.2 COZAAR IN THE HYPERTENSION MARKET

Please see Addendum A for background on COZAAR.

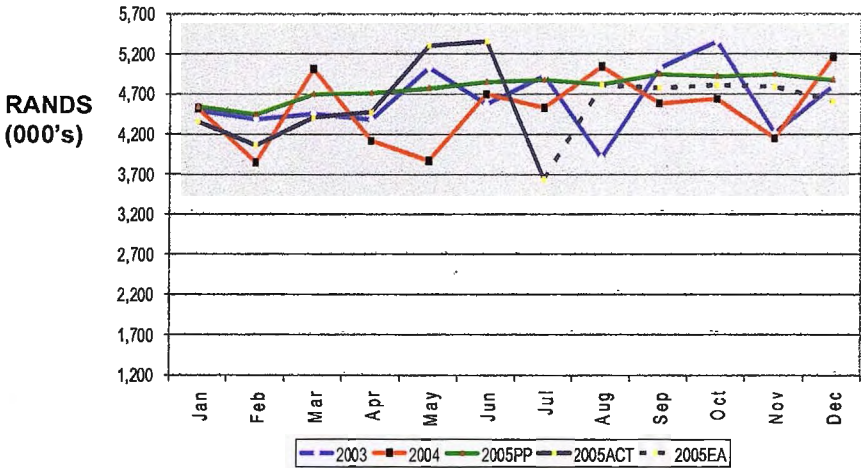
Figure 3.1 below, shows COZAAR sales over the last five years. Up until January 2004, the month that introduced new legislation and PMB, the COZAAR franchise had been growing steadily at a rate of 14% year-on-year. Sales have since flattened out in response to new legislation, PMB and restrictive managed health care reimbursement.



(Source: IMS, May TPM: 2005)

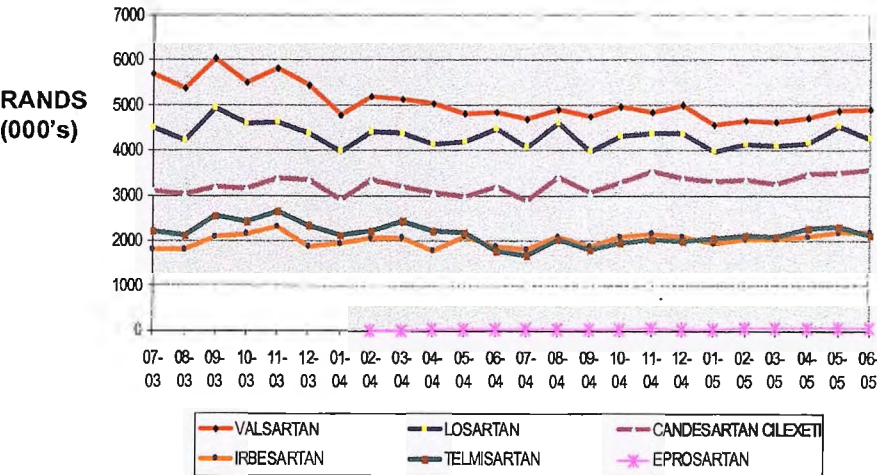
In spite of this COZAAR is still MSD's largest product now that VIOXX is gone. COZAAR currently contributes 20% to MSD's bottom line. COZAAR is expected to achieve R57.4 million over 2005, which represents a 6% growth over 2004 – see figure 3.2 below. Currently COZAAR holds a 6% market share in the total SA Hypertension Market and a 26% market share (ranked 2nd) in the constructed AIIA market – see figure 3.2 and 3.3 below.

Figure 3.2: COZAAR Franchise Sales, with 2005 estimate



(Source: IMS, July TPM: 2005)

Figure 3.3: Market Shares in AIIA class



(Source; IMS June TPM: 2005).

3.3 THE COZAAR CHALLENGE

Now with the loss of VIOXX, the COZAAR sales and marketing team have been set the challenge – to achieve an 8% growth in 2006, just months a way from patent expiration. COZAAR was originally projected to achieve R58 million over 2006 but an 8% growth would mean that this has been effectively raised to R62 million. This is indeed a huge challenge considering the fact that COZAAR is also operating in the most tightly regulated and restricted, crowded and most cutthroat segment of the SA pharmaceutical market – the Hypertension (C09) market.

3.4 THE COZAAR SWOT ANALYSIS

3.4.1 Strengths

Please see ADDENDUM A for all references to this section.

“COZAAR has proven Blood Pressure Lowering”

COZAAR and COZAAR COMP have provided excellent results in lowering blood pressure. In controlled trials, COZAAR lowered blood pressure comparable to other classes of antihypertensive therapy, including ACE inhibitors, calcium-channel blockers, beta blockers and diuretics. The results of a pooled meta-analysis of 51 published, randomized, controlled trials showed that COZAAR is highly effective in controlling blood pressure comparable to other angiotensin II antagonists. Other studies have shown that COZAAR provided consistent 24-hour blood pressure reduction.

“COZAAR has been proven to reduce Cardiovascular Morbidity and Mortality”

COZAAR is also an anti-hypertensive agent that has been proven in two Multi-center Landmark Trials, to have significantly reduced mortality and morbidity in patients with high blood pressure and specific co-morbidities.

In the RENAAL Trial, for the same reduction in blood pressure in hypertensive patients with Type 2 Diabetes and Micro/macro Albuminuria, COZAAR significantly reduced the primary composite endpoint of End Stage Renal Disease (ESRD), Doubling of Serum Creatinine or Death by 16% ($p=0.02$). COZAAR also significantly reduced the incidence of ESRD by 28% ($p=0.001$) and Doubling of Serum Creatinine by 25% ($p=0.006$). This was the first time that any product had proven to be superior to conventional antihypertensive therapies in reducing the incidence of ESRD in Type 2 Diabetic patients (Brenner BM et al. Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345:861-869).

In the LIFE Study, for the same reduction in blood pressure in hypertensive patients with ECG-LVH, COZAAR significantly reduced the primary composite endpoint of MI, death and stroke by 13% compared with atenolol ($p = 0.021$). COZAAR also significantly reduced the incidence of stroke by 24.9% compared with atenolol ($p = 0.001$). This was the first time ever that any antihypertensive had proven superiority over another active comparator (Dalh f B, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 2002; 359: 995-1003).

“The results of LIFE and RENAAL effectively influenced changes to the SA Hypertension Society’s Treatment Guidelines”

It is because of these two landmark studies that COZAAR has now been identified as a product with molecular specific pharmacological properties proven to save lives and improve quality of life. Accordingly the Angiotensin Receptor Blockers (ARBs) have recently been included on the SA Hypertension Society’s

Treatment Guidelines for first line and unconditional use in patients with hypertension and:

- (I). Type 2 Diabetes Mellitus with Micro/macro Albuminuria
- (II). Left Ventricular Hypertrophy (LVH) – See slide 2 below for the SA HT Societies Recommendations on Compelling Indications

ACT 131 has made provision for the use of newer classes of innovative ethical medicines that have been proven to reduce morbidity and mortality; or significantly improve quality of life. The innovative medicines alluded to are included onto the PMB treatment guidelines and PMB formularies, but restricted for use in what they call “Compelling Indications”. For companies like MSD who are fortunate enough to have innovative products like COZAAR, included onto these lists for use in specific patients, there is still an opportunity to leverage a focused market niche strategy based on differentiation. The challenge for MSD will be to capitalize on these provisions by developing very powerful marketing campaigns to leverage the relevant clinical data and differentiate COZAAR as the referenced AIIA on the treatment guidelines.

Figure 3.4: Recommendations on Compelling Indications (SA HT Society)

<u>Table 1V - Recommendations on Compelling Indications for a Specific Drug Class</u>	
Compelling Indications	Drug Class
• Angina • Prior MI or Coronary Artery Stenosis • Post MI • Heart Failure	• B-blocker or CCB (rate lowering preferred) • B-blocker and ACE1 (ARB if ACE1 intolerant) • B-blocker and ACE1 (ARB if ACE1 intolerant) • B-blocker and ACE1 (ARB if ACE1 intolerant) AND Aldosterone antagonist
• Left Ventricular Hypertrophy (confirmed by ECG)	• ARB (preferred) or ACE1
• Diabetes Type 1 or 2 with or without microalbuminuria or proteinuria	• ARB or ACE1 – usually in combo with a diuretic
• Chronic Kidney Disease	• ARB or ACE1 – usually in combo with a diuretic
• Isolated Systolic Hypertension • Pregnancy • Prostatism	• Low dose thiazide diuretic and/or long acting CCB • Methyl dopa, prazosin, CCB • α- blocker (not used in monotherapy for hypertension)

(Source: SA Hypertension Society Treatment Guidelines, SAMJ, March 2004, Vol.94, No.3)

3.4.2 Weaknesses

“COZAAR has not yet overcome the problem of “class effect” and as a result suffers the consequence of in-class substitution.”

According to the evidence, COZAAR should be the automatic choice in the treatment of hypertensive patients with Type 2 Diabetes and LVH; and this should relate to market share leadership in these market segments. However, this is not the case. COZAAR is ranked 2nd in market according to value and unit sales. In spite of LIFE, RENAAL and the South African Hypertension Societies Recommendations on Compelling Indications, the COZAAR sales and marketing team have failed to overcome the “class effect” argument which suggests that all AIAs are the same and that the proven benefits of COZAAR can be assumed for the rest in the class.

“COZAAR is too expensive”

Currently COZAAR is the most expensive AIA in the marketplace and sells at a single exit price of R167 excluding VAT. COZAAR correspondingly has a R33 premium over the cheapest product in the class. As a result, many customers choose to follow a “class effect” argument to justify their use of the cheaper AIAs when treating even those patients with compelling indications. One would think that recent product withdrawals like VIOXX from the Coxib class, BAYCOL from the Statin class and TROVAN from the Flouroquinolone class; would have put people off using this argument, but it has not. It would seem that the temptation to save money far outweighs the logic that motivates that products within classes may differ in efficacy and safety.

“COZAAR reps have too few calls and not enough time available per call to overcome the “class effect” and as a result, suffer the consequence of in-class substitution.”

One explanation for MSD's inability to differentiate COZAAR may relate to the fact that COZAAR reps are finding it more difficult to see their physicians and when they do, the time afforded to them is limited. Under these circumstances they are unable to effectively leverage the results of LIFE, RENAAL and the South African Hypertension Societies Recommendations on Compelling Indications; to change customer perceptions and behaviour. Presenting clinical trials is a complex and time consuming task; add to this the time necessary for persuasion, and one can see that 7 minutes is just not enough.

3.4.3 Opportunities

"9/10 medical aids now reimburse COZAAR without co-pay in patient with Compelling Indications i.e. hypertensive patients with Type 2 Diabetes and Micro/macro Albuminuria and/or evidence of Left Ventricular Hypertrophy (LVH)"

Figure 3.5: COZAAR Reimbursement Status

			A: In Compelling Indic's for AIIA (SA HT Guidelines)			B: In Compelling Indic's for ACE (SA HT Guidelines)		Extended Chronic Plan
			PMB - LVH on Echo/ECG	PMB - LVH only on ECG	PMB - T2DM + Macro/micro Albumin	Proof of failed ACE	A report of ACE intolerance	
1	Solutio Health F	30%	Full	Full	Full	Full	Full	Full
	Medscheme		Full	Full	Full	Full	Full	Full
2	Discovery	20%	Ask for ECG	Full	Full	Another class	Full	Full
3	Metropolitan	10%	Ask for ECG	Full	Full	Another class	Full	Full
4	Scriptpharm RN	8%	Full	Full	Full	Full	Full	Full
	Old Mutual		Full	Full	Full	Full	Full	Full
5	MediHelp	5%	Full	Full	Full	Full	Full	Full
6	Sovereign	5%	Ask for ECG	Full	Full	Another class	Full	Full
7	Medikredit RM	4%	AIIA Ref Price	AIIA Ref Price	AIIA Ref Price	AIIA Ref Price	AIIA Ref Price	Full
8	MxHealth	3%	Ask for ECG	Full	Full	Full	Full	Full
9	Resolution	3%	Full	Full	Full	Full	Full	Full
10	Providentia RM	2%	Full	Full	Full	Full	Full	Full
	Minimed		Full	Full	Full	Full	Full	Full

(Source: Data on file: Dr E. Ngobeni, MSD MHC SURVEY, 2005)

“Patients with Compelling Indications represent 20-40% of the hypertensive population in SA (1-2million patients); and COZAAR has the potential to dominate in this niche segment”

Based on the findings of a recent SA prevalence study conducted by Professor Rayner of the University of Cape Town, it is now estimated that approximately 30% of the SA hypertensive population have T2DM and 22% of them have Micro/Macro Albuminuria. It also estimated that 15-20% of the hypertensive patients have LVH, and there is a cross-over between these two patient groups. We can therefore make the educated assumption that COZAAR has compelling indication for first line use in 20-40% of all hypertensive patients. But because of new legislation and PMBs, medical aids have been empowered to enforce the use of protocols and formularies to exclude patients in the remaining 60-80% of the hypertensive population from using COZAAR (or any other AIIA). This has for obvious reasons intensified rivalry amongst AIAs in this niche segment of the hypertensive market. In order for COZAAR to achieve its growth targets, it will have to overcome the “class effect” and dominate in this niche segment, as it should.

“To help overcome problems relating to physician accessibility and the decline in rep productivity, technology-based solutions, such as e-Profiling, e-CME and e-Detailing, have arisen.”

If used appropriately, these initiatives can offer physicians with high-quality information in a convenient and interactive format. MSD can essentially use e-Profiling, e-CME and e-Detailing to increase the quality, reach, frequency and impact of their promotional messages regarding LIFE, RENAAL and the Compelling Indications. COZAAR could also benefit from the opportunity to reach difficult-to-see physicians outside of their busy practices, in the comfort of their own homes, when they have more time and are more receptive. Consequently MSD has begun integrating e-Marketing into their marketing plan, starting with the COZAAR e-Pilot – which is focused on differentiating the product based on evidence-based-medicine (LIFE and RENAAL).

“To help overcome problems relating to physician accessibility and the decline in rep productivity, the NCRA was established to serve as a vehicle for traditional CME and differentiation”

In order to capitalise on opportunities to differentiate, MSD has increased their investment in traditional CME. To this end, MSD established the National Cardiovascular Risk Academy in February 2004, to operate as their CME vehicle, through which they would promote the results of the LIFE and RENAAL trials.

3.4.4 Threats

“COZAAR faces the threat of both generic and in-class Substitution”

The practice of generic substitution in uncomplicated hypertensive patients has also had a significant impact on COZAAR. However, MSD has come to terms with the fact that in low risk patients, ethical treatment is unlikely and COZAAR has consequently been targeted at the high risk segments of the hypertensive market.

A more concerning issue for MSD, however, is the threat of substitution by a cheaper AIIA, in patients with compelling indications. These patients should be using COZAAR and yet they are forced by medical aids to switch to cheaper brands within the class or face the penalty of co-payment. This practice is illegal and is being contested; however, until the problem is resolved this practice is impacting negatively on COZAAR sales.

Consequently, MSD has begun focusing on different ways to differentiate COZAAR from other AIIAs at a medical aid level. Dr Tinnie Stander and Prof Naidoo, both pharmaco-economists are busy developing a economic report on COZAAR and the potential downstream cost benefits that can be achieved through primary prevention of stroke. When this report is completed MSD will meet with key decision makers within the larger medical aids, to determine the most appropriate way forward.

3.5 SUMMARY OF THE COZAAR 2006 MARKETING PLAN

3.5.1 Sales Objective

To achieve sales of R62 million by December 2006. This represents an increase of 8% over sales of R 57.4 million the franchise EA for 2005. This can be achieved if:

- COZAAR achieves R21 million (3% over sales of R20.3million - EA 2005)
- COZAAR Comp & FORTZAAR achieves R41 million (13% over sales of R37.1 million - EA 2004)

3.5.2 Market Share Objective

- To achieve a 28% market share in the AIIA market by December 2006. This represents a 2% point increase vs. a market share of 26% achieved in June 2005.
- To achieve a 7% market Share in the AHT market by December 2006. This represents a 1% point increase vs. a market share of 6% achieved in June 2005.

3.5.3 Behavioural Objective

- Influence physicians to actively screen for LVH and Micro/macro Albuminuria in both new and existing HT patients
- Influence physicians to prescribe Angiotensin II Receptor Blockers (AIIAs) ahead of ACE Inhibitors (ACEIs) in patients with LVH and/or T2DM
- To influence physicians to “automatically” prescribe COZAAR ahead of other AIIAs for their HT patients with T2DM / LVH because of the superior risk reduction for Cardiovascular Morbidity and Mortality, Stroke and End Stage Renal Disease (ESRD)
- To influence physicians to actively switch to, or combine with COZAAR ahead of other ACEIs and AIIAs in uncontrolled hypertensive patients.

3.5.4 Tactical Imperatives

- Have a spontaneous awareness of ESRD protection afforded by COZAAR of 50% by December 2006 – Baettard Mansley Research
- Increase recall of Stroke Risk reduction message in patients with LVH from 46% to 55% by December 2006 – Baettard Mansley Research
- Sales force implementation – Achieve average frequency of 7 in High potential AllA users (December 2006) – GeneSys Reports

3.5.5 Key Success Factors

- Attain 100% reimbursement status for compelling indications
- Maximise efforts and optimize resources – 9 point grid & ERA Targeting
- Leverage the NCRA to rally Key Opinion Leader Support for COZAAR
- Leverage the internet and emerging technologies (as pilot roll-out) to improve our understanding of our customers (improve profiling), and thereby...
 - ⊖ Improve on customer relations
- Leverage the internet and emerging technologies (as pilot roll-out) to improve cost efficiencies in COZAAR marketing - just 18 months from patent expiration, and decline phase.
- Leverage the NCRA as well as the internet and emerging technologies (as pilot roll-out) to improve the reach, frequency and impact of the promotional message, which will...
 - ⊖ Focus on Type 2 diabetes and EOP (COZAAR = RENAAL) to increase switch to COZAAR
 - ⊖ Focus on LVH and stroke risk reduction (COZAAR = LIFE) to increase switch to COZAAR

- ⊖ Focus on Uncontrolled hypertensive patient on >2 agents to add on / switch to COZAAR
 - ⊖ Differentiate COZAAR from the competition, and thereby...
 - ⊖ Increase Depth of prescriptions amongst High Potential general physicians and Specialists
 - ⊖ Accelerate growth vs. competition
- Leverage COZAAR new branding elements to maintain “top of mind awareness”

3.5.6 COZAAR Positioning

For

⇒ High potential general physicians and specialists treating hypertension

□ COZAAR is

- ⊖ The only antihypertensive agent that has demonstrated both a reduction in ESRD in hypertensive patients with T2DM and a superior stroke risk reduction, beyond effective BP control, in patients with LVH
- ⊖ A powerful partner in helping physicians in their effort to reduce uncontrolled HT

□ Because COZAAR provides

- ⊖ Useful downloads included downloadable versions of Clinical Trials and Slide Shows. Physicians were also able to access and print many of the graphic resources by clicking on the images. Powerful blood pressure reduction in uncontrolled hypertensive patients
- ⊖ Provides a proven dosing regimen (50mg, 50/12.5mg, 100/25mg)

3.5.7 Segmentation and Targeting

COZAAR Sales reps will target only on the following physician segments:

- ⊖ Priority 1 physicians: High Potential Medium Share
- ⊖ Priority 2 physicians: High Potential High Share
- ⊖ Priority 3 physicians: High Potential Low Share

Figure 3.6: Segmentation and Targeting - 9 Point Grid

	Metrics	Low Share	Medium Share	High Share
High Potential	Brick Count	40	40	17
	# Cards	22	22	4
	# Phys	44	61	12
	# GPs	1053	1120	458
	Market Size (Value)	33950890(21%)	34991537(22%)	11451809 (7%)
	Market Growth / Customer	R 7,388.54	R 6,942.42	R 16,970.37
	Own Sales	7195003 (17%)	10091331(24%)	4266063 (10%)
	Own Growth / Customer	R 1,261.24	R 1,185.09	R 2,896.88
	1:1 Details	1325	1331	614
Medium Potential	Brick Count	59	41	27
	# Cards	41	12	7
	# Phys	89	38	18
	# GPs	1507	919	571
	Market Size (Value)	22486253 (14%)	15503232 (10%)	10225119 (6%)
	Market Growth / Customer	R 1,298.09	R 2,129.12	R 3,427.57
	Own Sales	4657754 (11%)	4441223 (11%)	3923519 (9%)
	Own Growth / Customer	R 56.59	R 92.81	R 149.41
	1:1 Details	1348	1095	579
Low Potential	Brick Count	114	47	41
	# Cards	19	4	6
	# Phys	78	16	17
	# GPs	2238	822	725
	Market Size (Value)	17905707 (11%)	7770433 (5%)	6517505 (4%)
	Market Growth / Customer	R 684.51	R 1,864.83	R 2,113.08
	Own Sales	3316272 (8%)	2243511 (5%)	2500635 (6%)
	Own Growth / Customer	R 25.89	R 70.55	R 79.94
	1:1 Details	1451	617	605

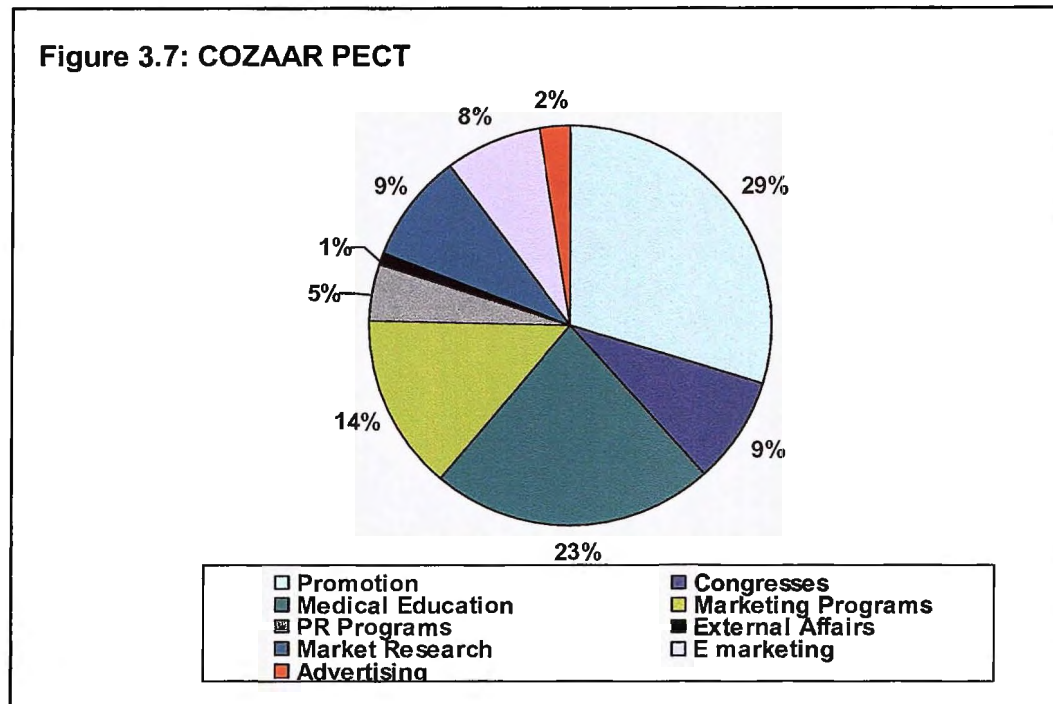
(Sources: IMS, Sands, June 2005; Medpages, June 2005; MSD Genesys 2005 update)

While the COZAAR promotional message will target the following patient segments:

- Patients that have one or both of the Compelling Indications, namely;
 - ⊖ Hypertensive patients that have Type 2 Diabetes and Micro/macro Albuminuria
 - ⊖ Hypertensive patients that have evidence of LVH

- Patients with uncontrolled hypertension who are already on two or more antihypertensives

3.5.8 The Marketing Budget – R5.3 million



(Source: COZAAR Marketing Plan 2006)

3.6 THE PROBLEM STATEMENT REVISITED

MSD has traditionally promoted their medicines via traditional channels that included: sales reps, medical journals and continued medical education (CME) seminars. The MSD sales force is large in comparison to other pharmaceutical companies and comprises mostly of university and college graduates / undergraduates. These employees are equipped with the necessary disease management training, product knowledge, selling skills and marketing support to empower them to out-think and out-manoeuvre their competition. It is also

important to note that at MSD the sales force is still regarded as the most effective promotional resource and accounts for over 60% of the company's marketing costs. However, recent sales force feedback and recent call report data (call rates, reach and frequency metrics), suggest that in spite of the value they add, doctors are unable to give MSD sales reps the time and attention they require to develop relationships and to effectively promote their products. The increasing number of "no see" visits and "reminder" details recorded; suggests that the sales force no longer wield the influence of relationships and promotional power they once did. The low frequency associated with limited opportunities has resulted in larger intervals between sales calls, shorter call durations and higher costs associated with travelling and waiting. The challenges facing the sales rep have always related to physician accessibility, time and the relevance and quality of the message, but it is clear that these barriers are higher now than before.

COZAAR sales reps, in particular, also face an even greater challenge. Legislation and MHC restrictions have reserved (niched) COZAAR for high risk patients with Compelling Indications, which has effectively reduced their target patient segment. As a result they have had to become more focused in their efforts to call on the very busy and difficult-to-see, high potential physician segments; who see such patients. These physicians are also typically targeted by all of the other companies. The end result is that the quality and frequency of the COZAAR reps detailing sessions is dropping and correspondingly the reps are finding it more and more difficult to differentiate COZAAR using LIFE, RENAAL and the SA Hypertension Society's Recommendations on Compelling Indications.

In the case of conventional detailing, the personality and knowledge of the sales rep will often constitute an advantage, but this can also make it difficult for the COZAAR marketing and product managers to ensure that their promotional messages are communicated consistently throughout the sales force.

Finally, there has been a tendency for MSD sales reps to classify and target physicians incorrectly. In many situations it has been noted that sales reps have categorised physicians as being A-physicians, not according to their potential to

use high amounts of the product, but according to their accessibility. This has lead to serious inefficiencies in sales and marketing activities at MSD and in the COZAAR business unit.

So the question remains - "If time in front of the physician is becoming more difficult for the COZAAR rep to achieve, would a strategy that integrates e-Profiling and e-Detailing into the sales and marketing process, not offer multi-channel synergies that will provide MSD with more opportunities to differentiate COZAAR and thus provide COZAAR with a competitive advantage over its competitors?" (Burgess, 2005)

3.7 CHAPTER SUMMARY

The COZAAR, SINGULAIR, FOSAMAX and EZETROL sales and marketing teams; that market MSD's remaining blockbusters, are now faced with the challenge of having to deliver even greater growth over 2006/7 than was originally anticipated, in order to fill the revenue void left behind by the VIOXX withdrawal. Only in this way will MSD be able to deliver on their long range targets and avoid downsizing over the next 2 years. To fully exploit the potential of COZAAR, MSD reps will have to differentiate it from substitutes using LIFE, RENAAL and the SA Hypertension Society's Recommendations on Compelling Indications. However, time in front of the physician is becoming more difficult for the COZAAR rep to achieve and correspondingly the reps are finding it more and more difficult to differentiate COZAAR. Consequently MSD has identified e-Profiling and e-Detailing as a possible solution to this dilemma.