TITLE

An Evaluation of the Efficacy and Safety of Meprobamate in Combination Analgesics and the Likely Economic Impact of its Withdrawal

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Research Report

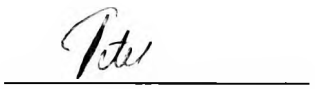
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Science (Medicine) in Pharmaceutical Affairs

December 2002

Johannesburg

DECLARATION

I Amanda Peter declare that this research report is my own work. It is submitted in partial fulfillment of the requirements of the degree Master of Science (Medicine) in Pharmaceutical Affairs, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.



Amanda Clare Peter

December 2002

DEDICATION

In memory of my beloved Mother

Bernadette Peter

and

in gratitude to all my family.

ABSTRACT

South Africa has the highest number of registered medicines containing meprobamate in combination analgesics and is the only country that markets a combination that includes paracetamol, caffeine and codeine. In November 1998 the Medicines Control Council issued a circular (11/98) to the Pharmaceutical Industry requesting evidence that meprobamate contributes meaningfully to the therapeutic effect in combination analgesics and asked for comment on the risk-benefit ratio.[1]

The aim of the study was to evaluate the efficacy and safety of meprobamate in combination analgesics and the likely economic impact of its withdrawal.

A literature search was conducted for studies published on meprobamate in combination analgesics. The databases searched included Embase, Medline and Toxbase.

The literature search found 9,244 publications for meprobamate, which was narrowed down to 180 publications of which only 10 were for combination analgesics containing meprobamate. On analyses, none of these trials conformed to the ICH guidelines for Good Clinical Practice (1st April 1997).

The analyses of these trials suggested that neither the efficacy nor the safety of meprobamate in combination analgesics was clearly demonstrated.

To assess the likely economic implication of the withdrawal of these products from the South African market, IMS data was collected for the period 1992 to 2001. The amount and Rand value of meprobamate containing analgesic dosage units sold on an annual basis was calculated and plotted against each year.

The amount and Rand value of all prescription only non-narcotic analgesic dosage units sold for the year 2001 was calculated as well as the loss/gain to each Company in the event that Meprobamate containing products are withdrawn from the South African Market.

In December 2001, (10,7%) of the whole Non Narcotic Analgesic market was spent on Meprobamate containing products. Ten Companies would gain in profits and 8 would loose if patients switched to another prescription only Non Narcotic Analgesic, in the scheduling category of 3 to 5 instead of using a meprobamate containing analgesic. In particular Adcock Ingram Healthcare stood to gain on average around R182,3 million, Aspen Pharmaceuticals on average around R13,6 million and Janssen Pharmaceuticals on average around R8 million.

If patients switched to another Non Narcotic Analgesic medicine in the scheduling category from 1 to 5, which includes over-the-counter medicines, 23 Companies would gain and 8 would loose. In particular Adcock Ingram Healthcare stood to gain on average around R38,5 million. Aspen Pharmaceuticals stood to loose on average around R8,5 million and Janssen Pharmaceuticals stood to gain on average around R1,6 million.

The overall economic impact of the withdrawal of Meprobamate containing products on the Pharmaceutical Industry would be positive rather than detrimental.

ACKNOWLEDGEMENTS

I am grateful to the following without whose assistance this research would not have been possible:

- Prof. Indres Moodley my supervisor for his guidance, suggestions, advice and support.
- Chris Muller for all his help in the computer analysis of data.
- Anita V.D Merwe and Marlene Da Silva of IMS Health (Pty) Ltd for kindly allowing me to access and use their data on marketing statistics.
- The Librarians at Wits medical school library for their assistance in the use on the Dialogue Web and for ordering publications for me not kept by the Library.

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1. INTRODUCTION

1.1 Background to study

In November 1998 the Medicine Control Council (MCC) sent out a circular to the Pharmaceutical Industry requesting evidence that meprobamate contributes meaningfully to the therapeutic effect in combination analgesics and asked for comment on the risk-benefit ratio.[1]

This circular was prompted, in part, by a letter to the Chairman of the MCC from a pharmacist in the public health sector expressing concern over the continued availability of meprobamate in this context.

South Africa has a relatively large market for analgesics (circa R712 million a year) and meprobamate has been an ongoing subject of concern to drug regulatory authorities worldwide and also to the MCC.

The Pharmaceutical Industry responded by submitting a number of journal publications of trials and studies performed in the 1970's and 1980's using Meprobamate in combination analgesics.

The responses from the Pharmaceutical Industry were reviewed and reported to the MCC in July 1999 and essentially the conclusions reached were:[2]

- There is no evidence to support the efficacy of Meprobamate in analgesics.

- However, there are no compelling safety issues relating to its use at the low dose at which it is included in such combinations.

- Meprobamate containing analgesics require a prescription from a registered medical practitioner (Schedule 5) and the package insert carries warnings appropriate to the safety issues.

- The use of these analgesics should be discouraged through medical education.

1.2 Registered products containing Meprobamate

The December 2001 issue of MIMS lists 27 combination analgesic medicines containing meprobamate.[3] Over the period 1992 to 2001 there have been 30 different products containing meprobamate registered in South Africa. See Table 1

Product number 29 for purposes of confidentiality cannot be named only has sales data from IMS for the year 2001.[4,5,6,7,8,9,10,11,12,13] See Appendix C

Product number 30 is listed in the MIMS December 2001 issue .No sales data has been published for it by IMS in any of the years from 1992 to 2001.

The three products listed in Table 1 that are not listed in the December 2001 issue of MIMS are:

Briscopyn Tabs	27/2.8/0303
*Equagesic Tabs	1324
*Painrite Forte Caps	Q/2.9/242

Table 1: Products containing Meprobamate

Trade Name	Reg No.	Applicant	Combination Actives
Antipyn Forte Tab	Y/2.8/321	Garec	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Banpain Tabs	Y/2.8/51	Triomed	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Briscopyn Tabs	27/2.8/0303	Quatromed (Aspen)	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg

Trade Name	Reg No.	Applicant	Combination Actives
Equagesic Tabs	1324	Akromed	Meprobamate 150mg Ethoheptazine: 75mg Aspirin: 250mg
Goldgesic Tabs	27/2.8/0249	Ranbaxy	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Go-Pain Tabs	27/2.8/0137	PD Pharm	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Maxadol ForteTabs	X/2.8/412	Restan	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Megapyn Tabs	X/2.8/240	CompuPharm	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
*Meprogesic Tabs	B1421	Propan-Zurich	Paracet. 500mg Cod. Phos. 10mg Meprobamate 125mg
Mepromol Tabs	X/2.8/173	Propan-Zurich	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Nopyn Tabs	S/2.8/238	Rolab	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Noralget Tabs	Y/2.8/118	HMR (Aspen)	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
*Painrite Forte Caps	Q/2.9/242	Columbia (Aspen)	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. 48mg
Pynmed Tabs	X/2.8/298	Medpro	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Salterpyn Tabs	27/2.8/0574	Propan-Zurich	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
*Spectrapain Forte Caps	N/2.9/0281	Alliance	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. 48mg
Spectrapain Forte Tabs	29/2.8/0280	Genpharm (Alliance)	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg

Trade Name	Reg No.	Applicant	Combination Actives
Stilpane Tabs	M/2.9/2	Lennon Meds	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
*Stilpane Caps	B624	Lennon Meds	Paracet. 370mg Cod. Phos. 8mg Meprobamate 185mg
Stopayne Tabs	B866	Al Pharm	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. 32mg
*Stopayne Caps	C/2.8/15	Al Pharm	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. 48mg
*Supragesic Caps	F/2.9/141	Pharm Ent	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. 48mg
*Synaleve Caps	B/2.6.4/80	Mer-National	Paracet. 400mg Cod. Phos. 8mg Meprobamate 200mg
*Tenston Tabs	B1127	Covan	Aspirin 200mg Paracet. 200mg Cod. Phos. 10mg Meprobamate 150mg Caff. 30mg
*Tenston SA Tabs	E/2.8/86	Covan	Paracet. 200mg Cod. Phos. 10mg Meprobamate 150mg Caff. 30mg
*Tenston SA Caps	R/2.9/90	Covan	Paracet. 200mg Cod. Phos. 10mg Meprobamate 150mg Caff. 30mg
*Trinagesic Caps	B810	Propan-Zurich	Paracet. 400mg Cod. Phos. 8mg Meprobamate 200mg
Vacudol Forte Tabs	27/2.8/0231	Xixia	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Xeramax T-Tabs	28/2.8/0384	Xeragen	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg
Xerogesic Tabs	27/2.8/0076	Crown	Paracet. 320mg Cod. Phos. 8mg Meprobamate 150mg Caff. Anhydr. 32mg

* Denotes a combination different to that of: Paracetamol 320mg,
Codeine Phosphate 8mg,
Meprobamate 150mg,
Caffeine 32mg.

The doses of preparations containing meprobamate in combination with other active ingredients ranges from 125mg to 200mg per capsule/tablet. The majority of the combination preparations contain 150mg of meprobamate per capsule/tablet.[3]

1.3 Aim of Study

To evaluate the efficacy and safety of meprobamate in combination analgesics and the likely economic impact upon the Pharmaceutical Industry in South Africa, of its withdrawal.

1.4 Research Questions:

1: Is there evidence that Meprobamate contributes meaningfully to the therapeutic effect of the analgesic combination?

2: Does the risk/benefit ratio of the meprobamate combination warrant the continued marketing of these products?

3: What is the trend in sales of these meprobamate-containing analgesics and what is the financial % market share relative to the whole non-narcotic analgesic market and is the trend in sales increasing, decreasing or remaining stable.

4: What is the likely economic implication of the withdrawal of meprobamate containing combination analgesics from the market?

5. Should meprobamate in combination analgesic preparations continue to be allowed to remain on the South African Market?

2. Literature Review

2.1 Background

Meprobamate was synthesized as a potential muscle relaxant in 1951 and later it was developed as a longer acting successor to mephenesin.[14] Mephenesin had been tried in different types of psychiatric disorders, but its usefulness was limited because of its short duration of action and unreliable absorption. Over 1200 compounds were investigated before meprobamate was selected and its pharmacological properties were described, including the ability to allay anxiety.[14]

Meprobamate was introduced as an anti-anxiety agent in 1955 and this remains its only approved use in the United States.[15] Prior to 1950 the barbiturates were the drugs of choice for managing anxiety and sleep disturbance. In the mid 1950's, they were essentially replaced by Meprobamate (Equanil, Miltown) [14]. Meprobamate also became popular as a sedative-hypnotic drug[15] and within 2 years after its introduction it was very widely prescribed.[14]

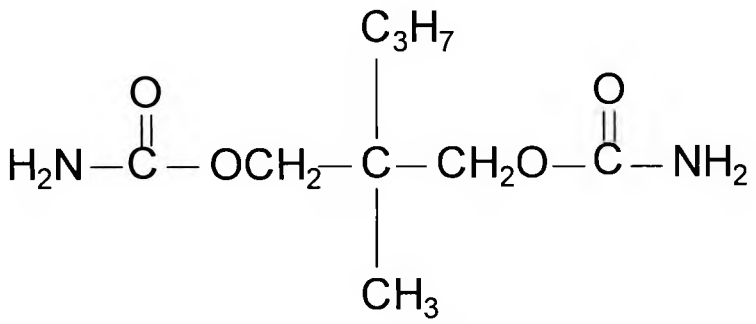
The question of whether or not the sedative and anti-anxiety actions of meprobamate differ remains unanswered, and clinical proof for the efficacy of meprobamate as a selective anti-anxiety agent in patients is lacking.[15]

2.2 Pharmacology

2.2.1 Chemistry and Structure-Activity Relationship

Meprobamate is a bis- carbamate ester;(2- methyl –2 – n – propyl –1,3 – propanediol dicarbamate) with the following structural formula:

$C_9H_{18}N_2O_4$=218.3



The substitution of a butyl group in place of a hydrogen on one of the carbamyl nitrogen atoms produces *tybamate*, a shorter-acting anti-anxiety agent. Isopropyl substitution at the same position results in *carisoprodol*, a muscle relaxant.[14]

2.2.2 Pharmacological Properties

The properties of meprobamate might be characterised as being intermediate between those of the barbiturates and the benzodiadepines.[16] They bear some resemblance to those of the benzodiazepines, but the drug has a distinctly higher potential for abuse and has less selective anti-anxiety effects.[17]

Although meprobamate can cause widespread depression of the CNS, it does so unevenly; there is considerable selectivity in its influence on various CNS functions, but it does not cause anesthesia.[16]

Meprobamate can depress polysynaptic reflexes in the spinal cord without affecting monosynaptic reflexes, and is more selective than barbiturates in this respect. This effect is thought to contribute to its muscle relaxant properties, although supra-segmental loci of action cannot be discounted. With clinical doses in man, the muscle relaxant effects are negligible, although there may be some decrease in spasm a result of a lessening in anxiety. Meprobamate does not appear to modify the effects of GABA-ergic inhibitory pathways and does not affect presynaptic inhibition in the spinal cord.[16]

In man, meprobamate suppresses absence seizures, but it may aggravate tonic-clonic and myoclonic epilepsy. Generalized seizures frequently occur as the result of abrupt withdrawal from chronic use of large doses.[16]

The drug inhibits a variety of responses to hypothalamic stimulation and shortens electrical after discharges in the limbic system; it also suppresses amygdalohippocampal-evoked potentials in doses that do not affect the arousal response evoked by the stimulation of the reticular formation of the brain stem. Despite these selective experimental effects, which are usually thought to correlate with anti-anxiety effects in man, clinical proof of efficacy as a selective anti-anxiety agent is lacking.[16]

2.2.3 Pharmacokinetics

Meprobamate is well absorbed when administered orally: Peak concentrations in plasma are reached in 1 to 3 hours. There is little binding to plasma proteins[17] and it is uniformly distributed in the body.[14]

The half-life of a single dose in plasma ranges from 6 to 17 hours, but it has been reported to be as long as 24 to 48 hours during chronic administration; the kinetics of elimination may be dependent on the dose. Meprobamate can induce some hepatic microsomal enzymes. It is not clear whether the drug induces the enzymes responsible for its own metabolism.[17]

Meprobamate is extensively metabolized in the liver by hydroxylation on the propyl group to yield the inactive metabolite [2 – methyl –2 –(ß–hydroxypropyl) –1,3-propanediol dicarbamate] and also by N-glucuronidation of the parent drug. It is excreted in the urine mainly as the inactive hydroxylated metabolite and its glucuronide conjugate. About 10% of the drug is excreted in an unchanged form in the urine[14] It diffuses across the placenta and appears in breast milk at concentrations up to 4 times those in maternal plasma.[18]

2.2.4 **Therapeutic Uses**

Even though meprobamate is currently approved for use only as an anti-anxiety agent, it is also used as a hypnotic agent in the treatment of insomnia. It has been advocated for hypnotic use in geriatric patients, for whom it has been reported to be as effective as flurazepam and flunitrazepam [19,20], more predictable than chloral hydrate, as well as being subject to fewer dosage problems than barbiturates and probably flurazepam.[16]

Meprobamate is a carbamate with hypnotic, sedative and some muscle relaxant properties, although in therapeutic doses its sedative effect rather than a direct action may be responsible for muscle relaxation. It has been used in the treatment of anxiety disorders and also for the short-term management of insomnia but has largely been superseded by other drugs. Meprobamate has sometimes been used alone or in combination with an analgesic, in the management of muscle spasm and painful musculoskeletal disorders but such use is no longer considered appropiate.[18]

The usual anxiolytic dose is 400mg by mouth three or four times daily to a maximum of 2.4g daily. In elderly patients, no more than half the usual adult dose has been suggested.[18]

2.3 Toxicology

Drowsiness is the most frequent side effect of meprobamate. Other effects include nausea, vomiting, diarrhoea, paraesthesia, weakness, and central effects such as headache, paradoxical excitement, dizziness, ataxia, and disturbances of vision. There may be hypotension, tachycardia, and cardiac arrhythmias. Hypersensitivity reactions occur occasionally. These may be limited to skin rashes, urticaria, and purpura or may be more severe with angioedema, bronchospasm, or anuria. Erythema multiforme and exfoliative or bullous dermatitis have been reported.[18]

Blood disorders including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia have occasionally been reported.[18] Symptoms of porphyria may be exacerbated. There is a serious dependence risk with a typical withdrawal syndrome. Acute poisoning produces stupor, coma, convulsions, shock and circulatory and respiratory collapse. Usually blood concentrations of 100 to 200 *ug* per ml are associated with deep coma requiring intensive treatment. Concentrations above 200*ug* per ml are often fatal. Deaths have occurred at lower concentrations.[21]

The abuse of meprobamate has continued despite a substantial decrease in the clinical use of the drug.[22] *Carisoprodol* (SOMA), a skeletal muscle relaxant whose active metabolite is meprobamate, also has abuse potential and has become a popular "street drug" [23]Meprobamate is preferred to the

benzodiazepines by subjects with a history of drug abuse. After long-term medication, abrupt discontinuation evokes a withdrawal syndrome usually characterized by anxiety, insomnia, tremors, and frequently, hallucinations; generalized seizures occur in about 10% of cases. The intensity of symptoms depends on the dosage ingested.[22]

3. Methodology

3.1 Data Collection for Clinical Trials

The following databases were searched from Dialogue Web for all clinical studies of meprobamate in combination analgesics.

Database Name Searched:

- Biosis Previews (1969 –present (file 5)
- SciSearch – a Cited Reference Science Database –1990 (File 34)
- Dissertation Abstracts on line (File 35)
- Inside Conferences (File 65)
- Elsevier Biobase (File 71)
- Embase (1974 –present) (File 73)
- International Pharmaceutical Abstracts (File 74)
- Conference Papers Index (File 77)
- Manual, Alternative and Natural Therapy(TM) (MANTIS (TM) (File 91)
- JICST-Eplus –Japanese Science & Technology (File 94)
- Pascal (File 144)
- Medline (1966 –present) (File 155)

- Toxline (File 156)
- CAB Health (File 162)
- Allied and Alternative Medicine (TM) (File 164)
- Embase Alert (File 172)
- Pharm- line (File 174)
- Drug Information Fulltext (File 229)
- Analytical Abstracts (File 305)
- Derwent Drug File (1964-1982) 9 File 376)
- CA Search – Chemical Abstracts (1967 –present) (File 399)
- SciSearch – a Cited Reference Science Database –1974 –1989 (File 434)
- ESPICOM Pharmaceutical & Medical Device News (File 442)
- Drug Data report (File 452)
- Drugs of the Future (TM) (File 453)
- The Lancet (File 457)
- ExtraMed(TM) (File 467)

A separate search of PubMed was also carried out.

The Search Instructions; "All Databases in Pharmacology" – with the key word "Meprobamate". Using the key word meprobamate alone, 9244 publications were found. The search was further refined with the key words "meprobamate and analgesic", the number of publications found were 984.The search was further refined with "meprobamate and combination analgesics/compounds" and 181 publications were found.

Ten publications relating to clinical studies with regard to safety and efficacy of meprobamate in combination analgesics were identified.

The studies were analyzed according to the principles as laid out by the ICH Guidelines for Good Clinical Practice.[24]

3.2 ICH Guidelines

The scientific integrity of any trial and the credibility of any data from the trial depend substantially on the trial design. A description of the trial design should include:[24]

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including;

    (a) Randomization

    (b) Blinding

- A description of the trial treatment(s) and the dosage regimen of the investigational product(s).
- The expected duration of subject participation, and a description of the sequence and duration of all trials periods, including follow up , if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s), if any.

- Maintenance of trial treatment randomization codes and procedures for breaking codes.

- Selection and Withdrawal of Subjects;

    (a) Subject inclusion criteria

    (b) Subject exclusion criteria.

    (c) Subject withdrawal criteria

- Treatments of Subjects;

    (a) The treatment(s) to be administered, including the name(s) of all the products, the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow–up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

    (b) Procedures for monitoring subject compliance.

    (c) Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

- Assessment of efficacy

    (a) Specification of the efficacy parameters

    (b) Methods and timing for assessing, recording and analyzing of efficacy parameters.

- Assessment of safety

  (a) Specification of safety parameters

  (b) The methods and timing for assessing, recording, and analyzing safety parameters.

  (c) Procedures for eliciting reports of and for recording and reporting adverse event and concurrent illnesses.

  (d) The type and duration of the follow-up of subjects after adverse events.

- Statistics

  (a) A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).

  (b) The number of subjects planned to be enrolled. In multi-center trials, the numbers of enrolled subjects projected in each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

  (c) The level of significance to be used.

  (d) Criteria for the termination of the trial.

  (e) Procedure for accounting for missing, unused, and spurious data.

(f) Procedures for reporting any deviation(s) from the original statistical plan.

(g) The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

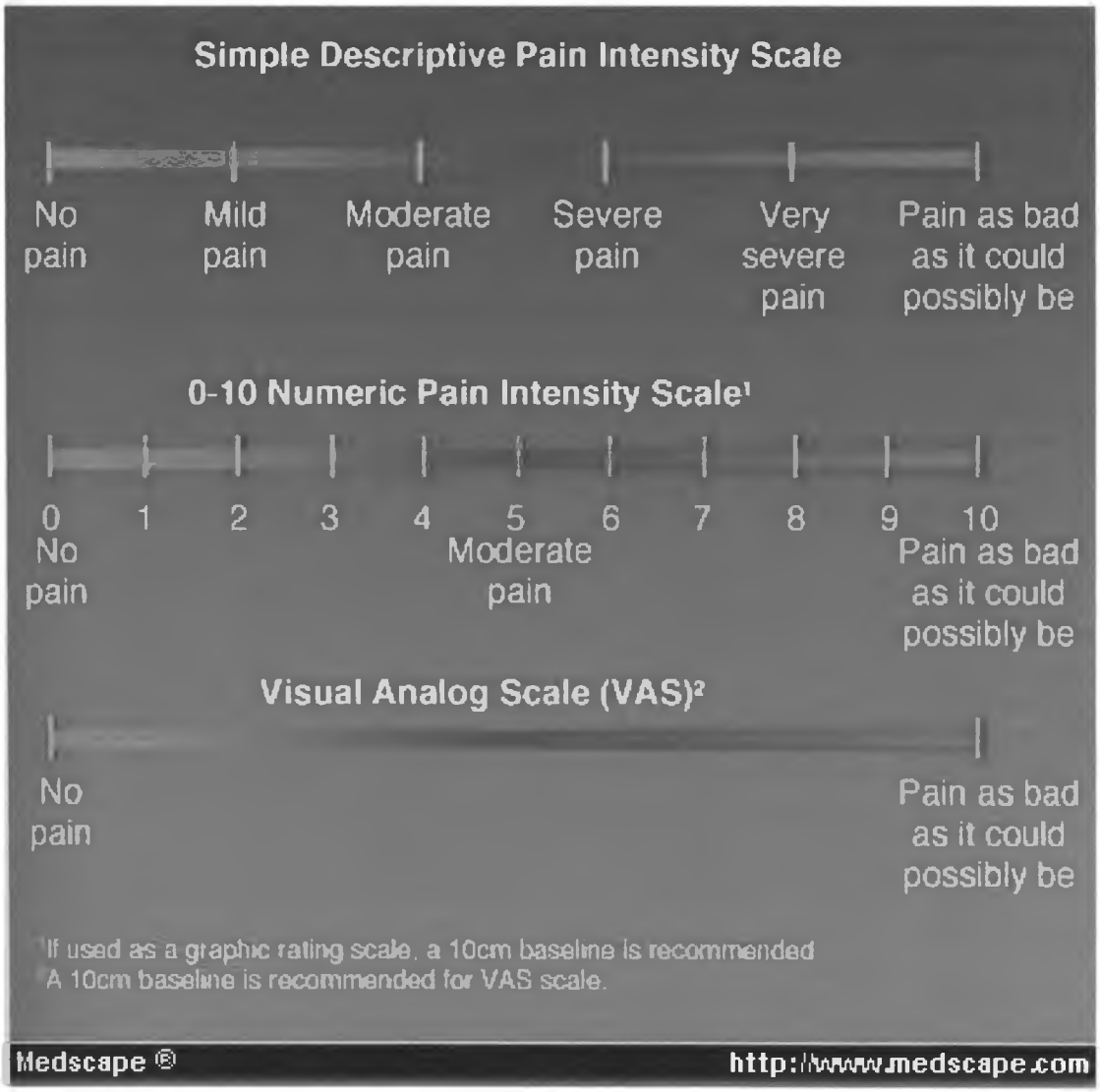
In trials that specifically deal with the relief of pain there are three commonly used self-report assessment tools[25] (Fig.1)

(1) Simple descriptive pain intensity scale

(2) 0-10 numeric pain intensity scale and

(3) Visual Analog Scale (Vas).

Figure 1: Models of pain intensity assessment



3.3 Data Collection for Sales of Meprobamate containing products

Data was collected from International Marketing Statistics (IMS) Health (Pty) Ltd on the annual sales of all Non-Narcotic Analgesics from the years 1992 to 2001,known as the N2B category in their data filing system.[4,5,6,7,8,9,10,11,12,13] A Non-Narcotic Analgesic refers to every analgesic/anti-inflammatory/antipyretic product scheduled from Schedule 1 to 5 as defined by Act 101 of 1965.

The data collected from IMS Health was sifted and all the products containing meprobamate in combination analgesics were identified and extracted from the collective group of Non-Narcotic Analgesics on an annual basis from 1992 to 2001.

A separate database was created for every product that has been registered in South Africa from 1992 to 2001 that contained meprobamate in combination with other analgesics.

A Microsoft Excel® spreadsheet database was created. The number of Units Sold, Pack Size and Rand Value and Company owner of each meprobamate-containing product that was on the market in each year from 1992 to 2001 was captured. The trade name of each product was assigned a number for reasons of confidentiality and in terms of the conditions of IMS Health (Pty) Ltd making available the information. See Appendix C

The total annual sales of all meprobamate containing analgesics, broken down to a per dosage unit, i.e. the total number of capsules and tablets sold was recorded for each year by multiplying the number of units sold per pack size. A correction for the population growth was made to gauge the growth/decline in sales on an annual per capita basis.

To correct for the population growth the annual population figures for SA. was obtained from the publication census for each of the years analyzed.[26] The factor to adjust for population growth to show increase/decrease in per capita consumption is as follows:

Population Growth Factor = Population in 2001 / Population in specific year

The adjusted, effective 2001 sales for any prior year is as follows:

Nominal Sales Volume x (Population Growth Factor)

The cumulative Rand value for all the meprobamate products was assessed for each year. A correction was made for the consumer price index and plotted against each year from 1992 to 2001 on the X-axis. See Figure 4

The cumulative Rand value for all the Non-Narcotic Analgesics was assessed each year. A correction was made for the consumer price index and plotted against each year from 1992 to 2001 on the X-axis. See Figure 5

Consumer Price Index was obtained for each year [27].The factor to adjust for inflation is as follows.

CPI growth factor = CPI in 2001 / CPI in specific year

The adjusted, effective 2001 Rand Value for any prior year is as follows:

Nominal Rand Value x (CPI growth factor)

3.4 Data collection for Economic Impact of Withdrawal

3.4.1 Broad Assessment

A Microsoft Excel® spreadsheet database was created. The number of Units sold, Pack Size and Rand Value and Company Owner of each non-narcotic analgesic product that was on the South African Market in the year 2001 was captured.

In the likelihood that all patients switched from the meprobamate containing analgesics to another prescription only Non-Narcotic analgesics with an even spread over the rest of the other products the Broad Overall Average Economic Impact would be as follows:-

The formula for the Broad Average Difference to the Pharmaceutical Industry is -

BD= Quantity of Meprobamate dosage units in 2001 X [Average price of a Non-Narcotic Analgesic dosage unit (Schedule 3 to 5, not containing meprobamate) - Average price of a Meprobamate containing analgesic dosage unit].

A dosage unit refers to either a capsule or a tablet.

3.4.2 Detailed Assessment

Data with respect to Units, Pack Size, and Rand Value was analyzed on the basis of each Company that owned Meprobamate containing products and each Company that owned any of the other Non-Narcotic Analgesics.

The average price for a Meprobamate containing analgesic dosage unit for each Company was determined.

The average price for a Non-Narcotic Analgesic dosage unit in the Schedule 3 to Schedule 5 category for each Company was determined (Meprobamate excluded.) See Table 3

The % Market Share in the Non-Narcotic Analgesic category from Schedule 3 to Schedule 5 (prescription only) excluding the meprobamate products for each Company was determined. See Table 3

The % Market Share in the Non-Narcotic Analgesic category from Schedule 1 to Schedule 2 (over-the-counter) was determined. See Table 4

The % Market Share in the Non-Narcotic Analgesic category from Schedule 1 to Schedule 5 was determined. See Table 5

Given that all the meprobamate containing analgesics were withdrawn and that the prescribers would switch their patients to another analgesic, the effect on each Company would be according to how each company captured the Non-Narcotic Analgesic Market from Schedule 3 to Schedule 5, Schedule 1 to Schedule 2 and from Schedule1 to Schedule 5.

The Economic Impact in terms of loss or gain to each Company, in the event of Meprobamate containing products being withdrawn from the South African drug market, would be according to the % Market Share each Company had in the Non-Narcotic Analgesic Market. Thus some Companies would stand to gain and others loose by the withdrawal of meprobamate containing analgesics.

Calculation for Economic Impact per Company.

A= Quantity of Meprobamate containing analgesic dosage units (capsules/tablets) for the year 2001 for each Company x Company average price for a meprobamate containing analgesic in 2001.

B= % Market Share of the Non-Narcotic Analgesic Market for each Company (within each scheduling category of S1 to S2, S3 to S5 and S1 to S5) x Total quantity of Meprobamate containing analgesic dosage units (capsules/tablets) for the year 2001 x the Company average price for a Non-Narcotic Analgesic in the year 2001. (based on each scheduling category of S1 to S2 ,S3 to S5 and S1 to S5)

C=B-A

C is the Rand Value gain/loss on switching from a Meprobamate containing analgesic to another prescription Non-Narcotic Analgesic for each Company.

3.5 Limitations of the research

Only 10 clinical studies on the efficacy and safety of meprobamate in combination analgesics were found, suggesting that very little research in this area has actually been done.

The Economic data from IMS Health (Pty) Ltd was captured from the Total Private Market. It is the pharmacy purchase price to all pharmacies, dispensing doctors and private hospitals/clinics and individual buying groups like Direct Medicines. The data is claimed to be 95% accurate by IMS Health (Pty) Ltd.

Meprobamate containing analgesics are only sold in a dosage unit of either a tablet or a capsule. In assessing the likely economic impact of its withdrawal, only the units, pack sizes and Rand value in dosage units of either a tablet or a capsule for the other prescription only Non-Narcotic Analgesics were captured. Suppositories, syrups and injections were not evaluated.

4. Results

4.1 Results of the Clinical Trials of Meprobamate.

The 10 publications of meprobamate in combination analgesics were analyzed and the outcome is summarized in Table 2.

Table 2 shows the analysis according to the author, title, objective, design, their conclusion and comments on the trial based on the ICH guidelines.

The first three of the 10 trials studied meprobamate in combination with aspirin and or ethoheptazine.[28,29,30] All three were double blind studies and contained a placebo and a drug comparator.

The other 7 trials studied meprobamate in combination with paracetamol and codeine and caffeine.[31,32,33,34,35,36,37] The trials were either of a single blind nature or an open study. There were no placebo's or other drug comparators in any of the trials.

Table 2 Summary Analyses of Clinical Trials.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Gilbert MM & Koepke HH (1973)	Relief of musculoskeletal and associated symptoms with meprobamate and aspirin: A controlled study.	To ascertain whether the combination of Aspirin and Meprobamate demonstrated the greatest improvement in both musculoskeletal and psychopathological symptoms.	A double blind study to compare the clinical response to a combination of meprobamate and aspirin (n=29), versus aspirin (n=29) and meprobamate (n=28) alone and a placebo (n=26). Duration of trial=3 days	The combination of aspirin and meprobamate demonstrated the greatest improvement in both musculoskeletal and psychopathological symptoms.	Not a validated model of pain assessment.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Scheiner JJ & Richards DJ (1974)	Treatment of musculoskeletal pain and associated anxiety with an ethoheptazine- aspirin-meprobamate combination (Equagesic): A controlled study.	To assess the efficacy of a combination containing ethoheptazine,aspirin and meprobamate versus a combination of ethoheptazine and aspirin versus meprobamate alone to control symptoms of pain and anxiety in patients who had not reacted to a placebo.	A double –blind cross over study. A-Aspirin/ethoheptazine B-Meprobamate C-Meprobamte/aspirin/ and ethoheptazine P-Placebo Duration of trial = 2 days. Wash out period=based subjectively when the patient felt pain and anxiety had returned to approximately the initial level of severity.	The ethoheptazine, aspirin and meprobamate combination was superior to the other treatments in the relief of pain and more effective than the ethoheptazine and aspirin combination in relieving anxiety.	There was no proper wash out period allowed between cross over dosing. There was no validated model for pain assessment.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Winkelman NW & Richards DJ (1975)	Double blind evaluation of an analgesic-tranquilliser combination for treating musculoskeletal pain associated with anxiety.	To assess the efficacy of a combination containing ethoheptazine,aspirin and meprobamate versus a combination of ethoheptazine -aspirin (analgesic) versus meprobamate (tranquilliser) and a placebo in the treatment of 90 anxious,psychoneurotic patients with musculoskeletal pain.	A double-blind, parallel, placebo controlled one-week study. Ethoheptazine,aspirin and meprobamate(n=21) Ethoheptazine –aspirin (n=23) Meprobamate (n=24) Placebo (n=23) Duration of trial=7 days.	The combination of ethoheptazine -aspirin (analgesic) demonstrated the greatest relief in the intensity pain while the combination of ethoheptazine,aspirin and meprobamate demonstrated the greatest relief in effect on anxiety.	Not a validated model of pain assessment. Contradicts the findings of Scheiner and Richards (1974)

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Fehler BM (1981)	Analgesic and Antipyretic effects of Stopayne Tablets in patients with influenza.	To assess the analgesic and antipyretic effects of Stopayne	A single-blind study. No placebo arm No other drug comparator. Duration of trial=1 day.	Stopayne is a useful analgesic agent in relieving the painful symptoms suffered by patients with influenza.	No pain assessment model mentioned. No drug comparator with paracetamol and codeine or with meprobamate alone or a placebo arm in the trial.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Stein A (1982)	Stopayne in the treatment of postoperative pain following gynaecological and obstetric procedures.	To assess the analgesic and muscle-relaxant effects of Stopayne tablets following gynaecological or obstetric surgery.	A single–blind study. No placebo arm No other drug comparator. Duration of trial=2 days	The clinical study provides evidence on the efficacy of Stopayne tablets as an analgesic for the relief of post-operative pain in patients who have undergone gynaecological and obstetric surgery.	No drug comparator with paracetamol and codeine or with meprobamate alone or a placebo arm in the trial.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Hossy SC & De Kock M (1982)	Treatment of postoperative pain with a combination analgesic: Stopayne Tablets.	To assess the analgesic effects of Stopayne.	A single-blind surgical study. Conducted in 2 centers, Johannesburg and Cape Town. Duration of trial = 6 months Patients assessed for 2 days following surgery. No placebo No other drug comparator	Demonstrates that the Stopayne formula is an effective analgesic for the relief of post-operative pain.	There is no comparator in the trial to demonstrate that meprobamate in the combination with paracetamol and codeine contributes meaningfully to the therapeutic effect of the Stopayne formula.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Nel G (1984)	Treatment of postoperative pain in orthopaedic patients with Stopayne tablets.	To assess the efficacy of Stopayne tablets in relieving pain in patients who had undergone orthopaedic surgical procedures after general anaesthesia.	An open study.(n=18) Duration of trial =2 to 5 days. No placebo No other drug comparator	The study provides evidence of the efficacy of Stopayne as a postoperative analgesic in patients who have undergone orthopaedic operations.	There is no comparator or placebo in the trial to demonstrate that meprobamate in the combination with paracetamol and codeine contributes meaningfully to the therapeutic effect of the Stopayne formula.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Earle JW (1984)	A study on the analgesic effects of Stopayne in patients who have undergone neurosurgery.	To assess the efficacy of Stopayne tablets in patients who had undergone either spinal or cranial surgery.	An open study. (n=29) Duration of trial =2 to 5 days. No placebo No other drug comparator	The study demonstrates the efficacy of Stopayne tablets in effectively controlling postoperative pain in neurosurgery.	There is no comparator placebo in the trial to demonstrate that meprobamate in combination with paracetamol and codeine contributes meaningfully to the therapeutic effect of the Stopayne formula.

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Bloch B et al (1985)	Analgesics for pain relief after gynaecological surgery.	To assess the efficacy of Stopayne and Baralgan HS in the relief of post operative pain.	A two-phase double-blind study. Phase 1 – double blind parallel way. Phase 2 –not relevant to the study. Stopayne-Compound A (n=84) Baralgan HS-Compound B (n=85) No placebo	There is little difference between the two drug combinations as regards relief of post operative pain.	There is no evidence to demonstrate that meprobamate in the combination with paracetamol and codeine contributes meaningfully to the therapeutic effect of the Stopayne formula, as there was no placebo or drug comparator with codeine and paracetamol leaving out the meprobamate with which to compare

Author	Title	Objective	Design	Conclusion of researches.	Comments based on ICH guidelines
Braun SA (1987)	Stopayne for postoperative analgesia in plastic surgery patients.	To assess the safety and efficacy of a combination analgesic, Stopayne tablets in patients who had under gone plastic surgery.	An open study.(n=23) Duration of trial = 2 days No placebo No other drug comparator	Stopayne was found to produce significant relief of pain 1 hour after administration of the tablets, the relief lasting for an average of 3,8 hours.	There is no comparator placebo in the trial to demonstrate that meprobamate in combination with paracetamol and codeine contributes meaningfully to the therapeutic effect of the Stopayne formula.

Gilbert and Koepke (1973)[28] in a single centre, 4 arm parallel design, used a 4-point verbal scale to demonstrate pain relief where the lowest number is indicative of the greatest relief of pain. The difference in the mean values for pain relief was not statistically significant.

Scheiner and Richards (1974)[29] in a double blind, 6 arm, cross-over design used a complicated way of measuring relief of pain and anxiety by combining the measurement for pain relief and anxiety. The measurements were taken 1, 2 and 3 hours after dosing. If there was no relief of pain and anxiety after the first, second and third hour, a value of 0 was given and if there was complete relief of pain and anxiety after the first, second and third hour, a value of 9 was given.

Each of the 6 groups received each type of permutation from the actives concerned to the placebo in a single dose only once. The patients were told to take their next different permutated dose of medication when, after the three hour assessment period was over, pain and anxiety had returned to approximately the initial level of severity. There was no proper wash out period allowed between cross over dosing. The carry over effects that could have occurred were not taken into account.

Winkelman JR and Richards DJ (1975)[30] in a single center, 4 arm, parallel design, measured the degree of pain relief on a 4-point scale of complete, marked, slight or none. Pain is a subjective perception and the same degree of pain could be considered slight by one person and marked by another. A validated model of pain assessment was not used.

The results of this study actually show that aspirin/ethoheptazine as a combination alone is better than meprobamate/aspirin/ethoheptazine in the relief of pain, while meprobamate/aspirin/ethoheptazine is better than aspirin/ethoheptazine for the relief of anxiety.

Fehler (1981)[31] in a single centre, single blind, 1 arm design of Stopayne Tablets, gave the patients a diary to record the degree of analgesia. How this degree of analgesia was measured is not reported. Also in this study there was no placebo control or control with another analgesic or a control versus paracetamol and codeine and caffeine without the meprobamate.

The design of this trial in relation to the results does not demonstrate that the addition of meprobamate in the formula of the compound gave any additive benefit and does not demonstrate that it is unsafe.

Stein. A (1982)[32] in a single centre, single blind ,1 arm design of Stopayne Tablets gave 23 out 40 patients who had undergone major pelvic surgery pethidine for the first 24 hours post operatively and then only 2 Stopayne tablets four hourly for the following 2 days. The results could be skewed due to a carry over effect from the previous day when the patient received pethidine. There is no placebo arm or drug comparator included in the trial. The trial does not demonstrate that the inclusion of meprobamate in combination with analgesics contributes meaningfully to the therapeutic effect of the analgesic combination.

Hossy and De Kock (1982)[33] in a two centered, single blind 1 arm design of Stopayne Tablets did not say how many assessments were actually made over the two day period for each patient as the patients were prescribed 2 tablets every 4 hours as and when required. Pethidine was administered for the first 24 hours, after which Stopayne was the only analgesic used. There was the possibility of a carry over effect from Pethidine to Stopayne. There was no placebo arm, no other drug comparator. The benefit of using Meprobamate in the Stopayne formula was not demonstrated.

Nel (1984)[34] in single center, 1 arm, open trial of Stopayne Talets, reported the population sample size was as little as 18 and not all patients remained in the study until day five without explanations for the drop out or withdrawal. There was no uniformity in the number of tablets each patient took daily. It was stated that the most frequently administered dose was 8 tablets on the first day and that most patients took 6 on the following day.

There was no placebo or another drug comparator in the trial to demonstrate the efficacy of meprobamate in the combination analgesic. There were no serious side effects reported.

Earle (1984)[35] in a single centre, open, 1 arm study of Stopayne Tablets conducted the trial where the dose for each patient was not uniform but *as required* to a maximum of two tablets four hourly. There was no placebo or drug comparator to measure against and no data to prove that meprobamate added any value to the combination of paracetamol, codeine, and caffeine.

Bloch *et al* (1995) [36] in a single center, double blind, 2 arm, parallel design comparing Stopayne Tablets with Baralgan HS Tablets reported that patients on Compound A (Stopayne) 19.0% took concomitant medication and 34,1% on Compound B (Baralgan HS) took concomitant medication rendering the results very unclear. The trial concluded there was very little difference between these two drug combinations as regards relief of postoperative pain. There was no evidence that Meprobamate contributed to the efficacy of the analgesic compound.

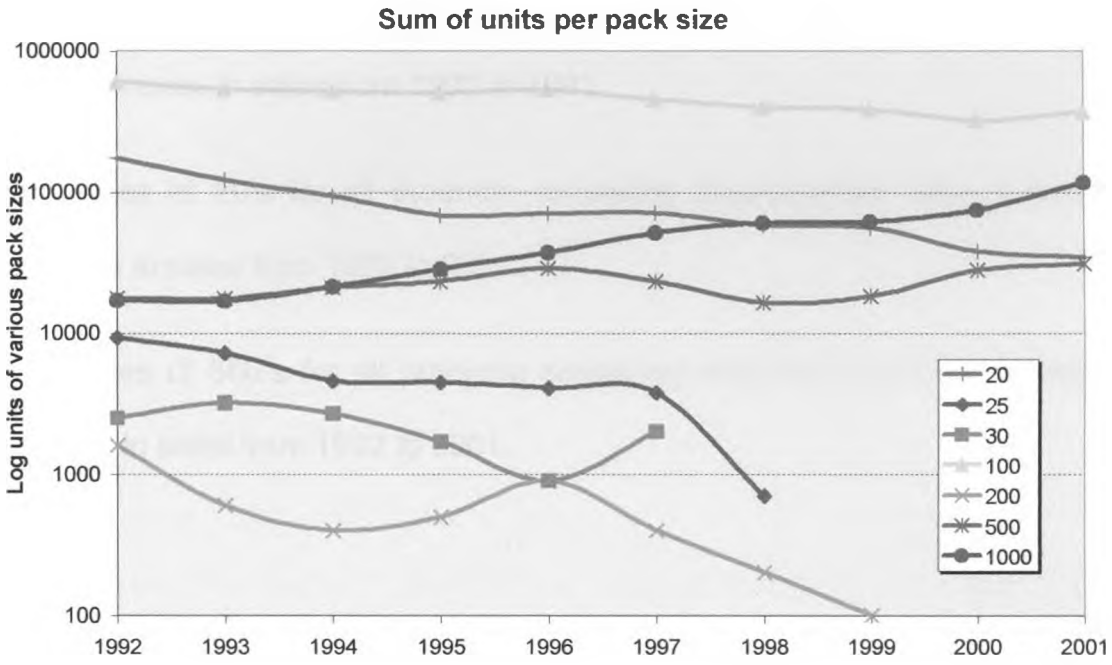
Braun (1987)[37] in a single centre ,open, 1 arm design of Stopayne Tablets reported that 91% of patients reported a decrease in the intensity of pain after the first day of the study and 96% of patients by the end of the second day. There was no placebo or drug comparator in the trial design and does not demonstrate that meprobamate in the formula helped to decrease the intensity of pain. There is no evidence that meprobamate was beneficial or harmful.

4.2 Sales Volume of Meprobamate

The analysis of the IMS database was conducted to calculate the volume of all meprobamate-containing products (see Table 1) sold in unit pack sizes of 20,25,30,100,200,500,1000 from 1992-2001.

The results are shown in Fig. 2

Figure 2: Sales of Units per pack size of all Meprobamate-containing Products.



The numbers in the box refer to the different pack sizes of all the meprobamate containing products.

The Y-axis refers to the cumulative sum of each pack size. The X-axis refers to each year.

The unit pack size of a 1000 for all products containing meprobamate has shown a slow steady increase in sales from 1992 to 2001.The greater the size of the unit pack size the cheaper the price in the dosage unit per capsule or tablet at the pharmacy purchase price. (See Appendix C).

The only meprobamate-containing product that was sold in a pack size of 25 was Equagesic Tablets. From 1999 onwards they have not been sold.

The 30's pack size for all products containing meprobamate was discontinued in 1997 and the 200's pack size for all products containing meprobamate in 1999.

Pack sizes of a 100 for all products containing meprobamate have a very slight decrease in sales from 1992 to 2001.

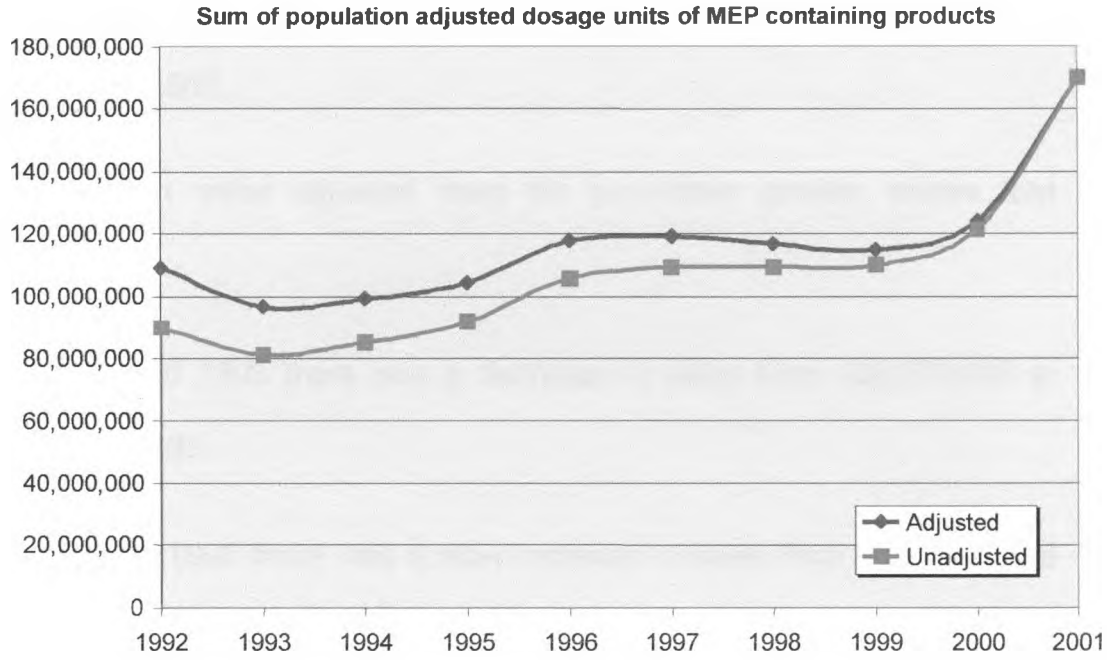
Pack sizes of 20's for all products containing meprobamate have a small decrease in sales from 1992 to 2001.

Pack sizes of 500's for all products containing meprobamate have a slight increase in sales from 1992 to 2001.

The analysis of the IMS database was conducted to calculate the volume of all meprobamate-containing products sold in actual dosage units i.e. the actual number of capsules and tablets sold from 1992-2001.

The results are shown in Fig. 3

Figure 3: Sum of Meprobamate Sales per dosage unit Capsule/Tablet in combination analgesics sold from 1992 to 2001



The pink line refers to the volume of capsules/tablets sold each year without correction for the population growth. The blue line shows the volume of capsules/tablets sold with an adjustment for the population growth.

- The volume in sales unadjusted (figure 3) for population growth shows that

- 1992 and 1993 there was a decrease in sales from 89,740,00 to 81,128,000.

- 1993 to 1999 there was a slow increase in sales from 81,128,000 to 109,921,200.

- 1999 to 2000 there was a more marked increase in sales and from 109,921,200 to 121,473,100.

- 2000 to 2001 a very marked increase in sales from 121,473,100 to 169,827,500.

The volume in sales adjusted does for population growth, shows that between:

- 1992 and 1993 there was a decrease in sales from 109,076,048 to 96,494,299.

- 1993 to 1996 there was a slow increase in sales from 96,494,299 to 117,795,614.

- 1996 to 1999 there was a slow decrease in sales from 117,795,614 to 114,792,060.

- 1999 to 2000 there was a more marked increase in sales from 114,792,060 to 124,135,303.

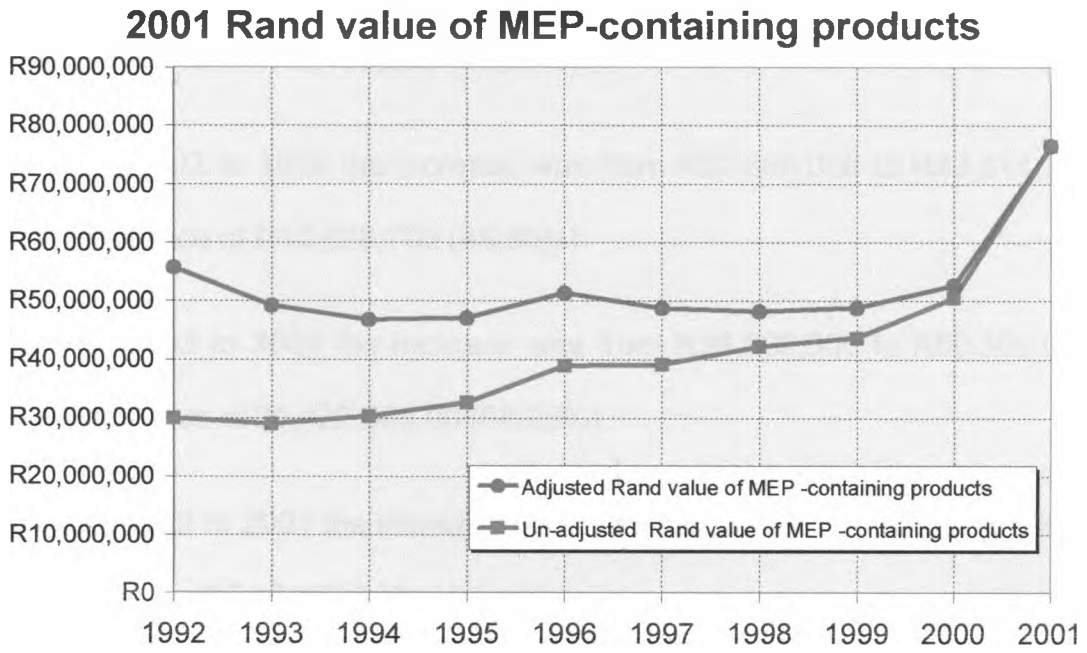
- 2000 to 2001 a very marked increase in sales.from 124,135,303 to 169,827,500.

4.3 The Rand Value of all Meprobamate Sales

The analysis of the IMS database was conducted to calculate the Rand Value of all Meprobamate containing products sold from 1992-2001.

The results are shown in Figure 4 The blue graph refers to the total Rand value, adjusted for the Consumer price index (CPI) for each year. The red graph refers to the total Rand value of all Meprobamate containing products sold per year without adjusting for inflation.

Figure 4: Rand value of Meprobamate-containing Products



The rand value in sales unadjusted (figure 4) for changes in the consumer price index shows that

From 1992 to 1993 there was a very slight decrease in rand value from R29,886,000 to R28,870,500. A difference of -R1,015,550 (-3,39%)

From 1992 to 1994 there was an increase in the rand value from R29,886,000 to R30,174,200. A difference of R288,200. (0,96%)

From 1992 to 1995 the increase was from R29,886,000 to R32,445,300. A difference of R2,559,300 (8,5%).

From 1992 to 1996 the increase was from R29,886,000 to R38,723,700 . A difference of R8,837,700 (29,57%)

From 1992 to 1997 the increase was from R29,886,000 to R38,983,500. A difference of R9,097,500 (30,44%) .

From 1992 to 1998 the increase was from R29,886,000 to R42,019,300 . A difference of R12,133,300 (40,59%)

From 1992 to 1999 the increase was from R29,886,000 to R43,514,700. A difference of R13,628,700 (45,60%)

From 1992 to 2000 the increase was from R29,886,000 to R50,308,000. A difference of 20,422,000 00 (68,33%)

From 1992 to 2001 the increase was from R29,886,000 to R76,348,000. A difference of R46,462,000 (155,46%)

The rand value in sales adjusted (figure 4) for changes in the consumer price index shows that between 1992 and 1993 there was a decrease in rand value from R55,634,689 to R49,054,819. A difference of -R6,579,870. (-11,82%)

From 1992 to 1994 there was a decrease from R55,634,689 to R46,662,256.A difference of – R8,972,433(-16,13%).

From 1992 to 1995 there was a decrease from R55,634,689 to R46,937,776.A difference of – R8,696,913 (-15,63%).

From 1992 to 1996 there was a decrease from R55,634,689 to R51,214,369.A difference of – R4,420,320 (-7,94%)

From 1992 to 1997 there was a decrease from R55,634,689 to R48,604,124.A difference of – R7,030,565 (-12,63%).

From 1992 to 1998 there was a decrease from R55,634,689 to R48,057,409.A difference of – R7,577,280 (-13,62%).

From 1992 to 1999 there was a decrease from R55,634,689 to R48,676,599.A difference of –, R6,958,090 (-12,51%).

From 1992 to 2000 there was a decrease from R55,634,689 to R52,579,411.A difference of – R3,055,278 (-5,49%).

From 1992 to 2001 there was an increase from R55,634,689 to R76,348,000.A difference of R20,713,311(37,23%).

From 2000 to 2001 there was a very marked increase in the rand value of the sales from R52,579,411 to R76,348,000. A difference of R23,768,589. (45.03%).This marked increase in rand value corresponds with the marked increase in the volume of sales from 2000 to 2001.

Summary:

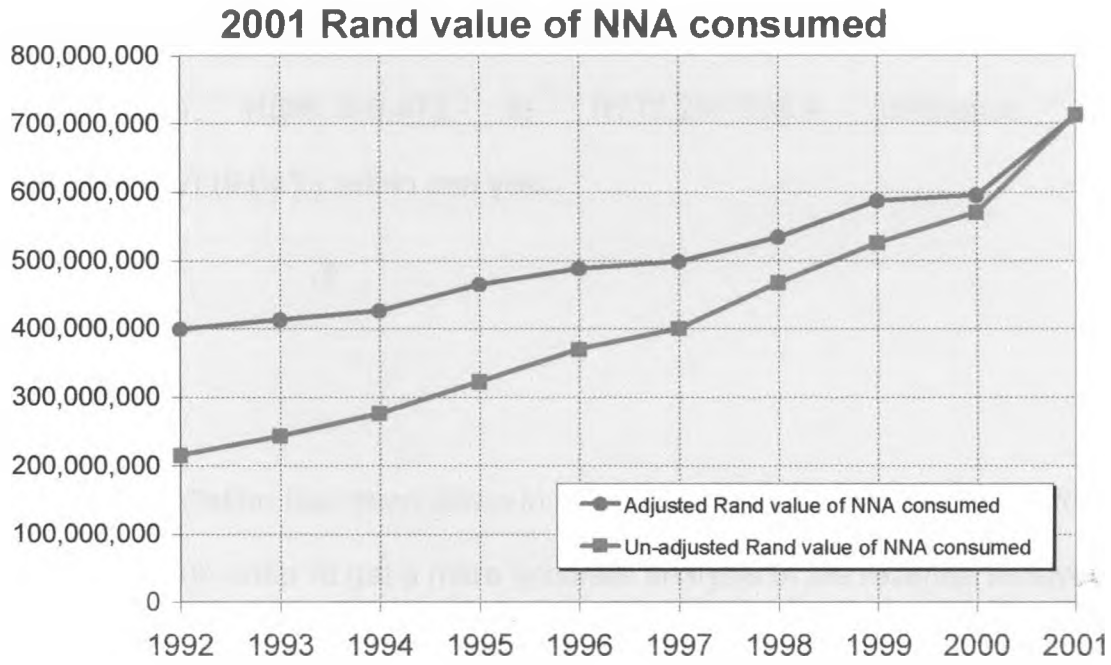
The rate of inflation has been taken in to account for the 10 year period from 1992 to 2001 in order to get a more accurate analysis of the revenue received by the Pharmaceutical Industry from the sale of these meprobamate containing products. The blue line on the graph illustrates that from 1992 to 1995 the revenue received by the Pharmaceutical Industry declined each year. In 1996 it instead increased. From 1996 to 1999 again revenue from the sale of these meprobamate containing products decreased. In 2000 and 2001 revenue from the sale of meprobamate containing products markedly increased.

4.4 Rand Value of all Non-Narcotic Analgesics from 1992 to 2001

The analysis of the IMS database was conducted to calculate the Rand Value of all the Non Narcotic Analgesics products sold from 1992-2001.

The results are shown in Figure 5 .The blue graph refers to the total Rand value, adjusted for the Consumer Price Index (CPI) for each year. The red graph refers to the total Rand Value of all Non-Narcotic Analgesics products sold per year without adjusting for inflation.

Figure 5: Rand value of Non-Narcotic Analgesics from 1992 to 2001.



The rand value in sales unadjusted (Figure 4) for changes in the consumer price index shows that between 1992 and 2000 there was a increase in the rand value from R213,986,500 to R569,666,000.A difference of R355,679,500 (166.22%)

From 2000 to 2001 there was a very marked increase in the rand value of the sales from R569,666,000 to R712,291,000. A difference of R142,625,000.(25.03%) within one year alone.

The rand value in sales of the adjusted graph that does take into account the consumer price index shows that between 1992 and 1999 there was a increase in the rand value from R398,349,474 to R587,077,390.A difference of R188,727,916.(47.37%)

From 1999 to 2000 the rand value increased from R587,077,390 to R595,386,473.A difference of R8,309,083 (1.41%) within one year.

From 2000 to 2001 there was a very marked increase in the rand value of the sales from R595,386,473 to R712,291,000.A difference of R116,904,527(19.64%) within one year.

Summary:

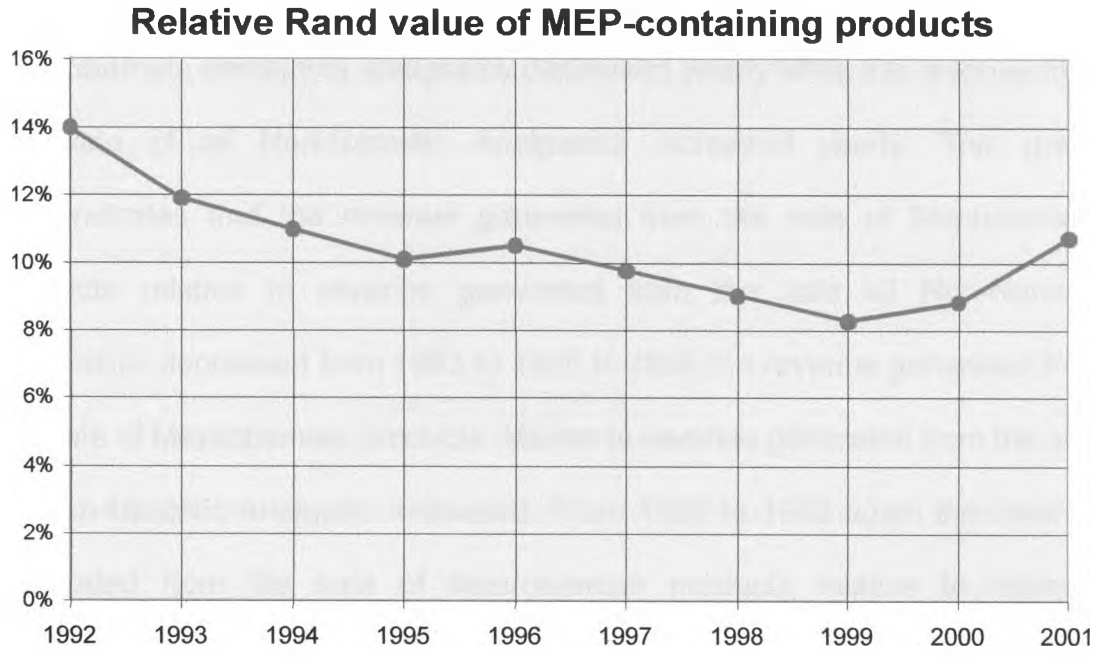
The rate of inflation has been taken in to account for the 10 year period from 1992 to 2001 in order to get a more accurate analysis of the revenue received by the Pharmaceutical Industry from the sale of all Non-Narcotic Analgesics from Schedule 1 to Schedule 5.The blue line on the graph illustrates that from 1992 to 2000 the revenue received by the Pharmaceutical Industry steadily rose by small increments each year. In 2001 the revenue received by the Pharmaceutical Industry from the sale of all Non-Narcotic Analgesics markedly rose with respect to the small increments of the proceeding years.

4.5 Percentage Market Share of Meprobamate

The analysis of the IMS database was conducted to calculate the relative % market share of all the meprobamate containing products in relation to the whole Non Narcotic Analgesic market from 1992-2001.

The results are shown in Figure 6 .The Y-axis is the % market share of all meprobamate-containing products plotted against each year from 1992 to 2001 on the X-axis.

Figure 6: Relative percentage value of Meprobamate-containing products in relation to the Non-Narcotic Analgesic market.



The overall percentage market share in the rand value of meprobamate containing products relative to the non-narcotic analgesics decreased from 13,9% in 1992 to 10,7% in 2001.

From the period 1992 to 1995, the % decline in market share went from 13,9% to 10,1%. From the period 1996 to 1999 there was a further decline in the % market share from 10,49% to 8,3%.

In contrast for the period 1999 to 2001 there was an increase in the market share from 8,3% to 10,7%.

Summary:

From 1992 to 1995 the Pharmaceutical Industry's revenue from the sale of meprobamate containing analgesics decreased yearly while the revenue from the sale of all Non-Narcotic Analgesics increased yearly. This graph demonstrates that the revenue generated from the sale of Meprobamate products relative to revenue generated from the sale all Non-Narcotic Analgesics decreased from 1992 to 1995.In 1996 the revenue generated from the sale of Meprobamate products relative to revenue generated from the sale all Non-Narcotic Analgesic increased. From 1996 to 1999 again the revenue generated from the sale of Meprobamate products relative to revenue generated from the sale all Non-Narcotic Analgesics decreased. From 1999 to 2001 the revenue generated from the sale of Meprobamate products relative to revenue generated from the sale all Non-Narcotic Analgesic increased.

4.6 Economic Impact

4.6.1 Broad Assessment

If the Medicines Control Council were to withdraw all products containing meprobamate in combination analgesics because of a lack of evidence that meprobamate contributes meaningfully to the therapeutic effect of the analgesic combination, then there are one of four options for patients that could have a negative/positive economic impact on the Industry.

1. The patient takes no other medication in place of the meprobamate containing products.

2. The patient switches to another prescription only non-narcotic analgesic.(S_3 to S_5)

3. The patient switches to an over-the-counter (OTC) non-narcotic analgesic.(S_1 to S_2)

4. Some patients switch to another prescription only non-narcotic analgesic.(S_3 to S_5) and some others switch to an over-the-counter (OTC) non-narcotic analgesic.(S_1 to S_2)

A broad assessment of the Economic Impact depending on the option.

Option 1 The patient takes no other medication in place of the meprobamate containing products.

The loss to the Industry in the year 2001 would be Rand value of the Meprobamate containing combination analgesic sales in 2001, which was R76, 348, 000.

Option 2 The patient switches to another prescription only non-narcotic analgesic.(S_3 to S_5)

BA=Broad Assessment

BA= [Quantity of Meprobamate dosage units in 2001] X [Average price of a prescription only Non-Narcotic Analgesic dosage unit.(S_3 to S_5) - Average price of Meprobamate containing analgesic dosage unit].

In the year 2001:

Number of Meprobamate dosage units =169,827,500

Rand Value of Meprobamate dosage units = R76, 348, 000

Therefore the average price of a Meprobamate dosage unit = R0, 45c

A dosage unit refers to either a capsule or a tablet.

In the year 2001:

Number of Non-Narcotic Analgesic dosage units, prescription only from Schedule 3 to Schedule 5 =130,225,360

Rand Value of the prescription only Non-Narcotic Analgesic dosage units (S_3 to S_5) = R220, 870, 000

Therefore the average price of a prescription Non-Narcotic Analgesic dosage unit = R1.70c

Using the formula BA= [Quantity of Meprobamate dosage units in 2001] X [Average price of a prescription only Non-Narcotic Analgesic dosage unit.(S_3 to S_5) - Average price of Meprobamate containing analgesic dosage unit].

Thus the broad assessment impact to the Industry would be :-

169,827,500 X (R1,70 - R0,45)

=169,827,500 X (R1, 25)

= +R212,284, 375

Thus on an overall average the Pharmaceutical Industry would stand to gain R212, 284,375 if all patients who took a meprobamate containing capsule/tablet, took instead another prescription only non-narcotic analgesic in the scheduling category of 3 to 5.

Broadly speaking, a patient switching from a meprobamate containing analgesic to another prescription non-narcotic analgesic on a one to one basis would have an overall positive impact on the Industry to the value of R212, 284, 375.

Option 3: The patient switches to an over-the-counter (OTC) non-narcotic analgesic.(S_1 to S_2)

BA=Broad Assessment

BA= [Quantity of Meprobamate dosage units in 2001] X [Average price of a OTC Non-Narcotic Analgesic dosage unit.(S_1 to S_2) - Average price of Meprobamate containing analgesic dosage unit].

In the year 2001:

Number of Meprobamate dosage units =169, 827, 500

Rand Value of Meprobamate dosage units = R76, 348, 000

Therefore the average price of a Meprobamate dosage unit = R0, 45c

In the year 2001:

Number of OTC Non-Narcotic Analgesic dosage units, from Schedule 1 to Schedule 2 = 676,990,400

Rand Value of OTC Non-Narcotic Analgesic dosage units= R 319,246, 000

Therefore the average price of an OTC Non-Narcotic Analgesic dosage unit = R 0, 47c

The broad assessment impact to the Industry would be:-

169,827,500 X (R0, 47- R0, 45)

=169,827,500 X (R0, 02)

= +R 3, 396, 550

Broadly speaking, a patient switching from a meprobamate containing analgesic to another OTC non-narcotic analgesic in the scheduling category of 1 to 2, on a one to one basis, would have an overall positive impact on the Industry to the value of +R 3, 396, 550.

Option 4: Some patients switch to another prescription only non-narcotic analgesic.(S_3 to S_5) while others switch to an over-the-counter (OTC) non-narcotic analgesic.(S_1 to S_2)

BA= [Quantity of Meprobamate dosage units in 2001] X [Average price of all Non-Narcotic Analgesic dosage unit.(S_1 to S_5) - Average price of Meprobamate containing analgesic dosage unit].

In the year 2001:

Number of Meprobamate dosage units =169,827,500

Rand Value of Meprobamate dosage units = R76, 348, 000

Therefore the average price of a Meprobamate dosage unit = R0, 45c

Number of all Non-Narcotic Analgesic dosage units, from Schedule 1 to Schedule 5 =807,199,760

Rand Value of all Non-Narcotic Analgesic dosage units=R540, 116, 000

Therefore the average price of all Non-Narcotic Analgesic dosage units = R 0, 67c

The broad assessment impact to the Industry would be:-

169,827,500 X (R0, 67- R0, 45)

=169,827,500 X (R0, 22)

= +R37, 362, 050

Broadly speaking, a patient switching from a meprobamate containing analgesic to another non-narcotic analgesic, either OTC or prescription, on a one to one basis, would have an overall positive impact on the Industry to the value of R37, 362, 050.

4.6.2 Detailed Assessment.

In order to determine the effect of the withdrawal of meprobamate containing products for each Company that owned a meprobamate product, data from the IMS database was extracted and all the Units, Pack Sizes and Rand Value was analysed on the basis of each Company that owned Meprobamate containing products and each Company that owned any of the other Non-Narcotic Analgesics from Schedule 3 to Schedule 5 and from Schedule 1 to Schedule 2. in the year 2001.

The average price for a Meprobamate containing analgesic dosage unit for each Company was determined. See Table 3

The average price for a Non-Narcotic Analgesic dosage unit in the Schedule 3 to Schedule 5 category for each Company was determined.(Meprobamate excluded) See Table 3

The average price for a Non-Narcotic Analgesic dosage unit in the Schedule 1 to Schedule 2 category for each Company was determined. See Table 4

The average price for a Non-Narcotic Analgesic dosage unit in the Schedule 1 to Schedule 5 category for each Company was determined.(Meprobamate excluded) See Table 5

The % Market Share in the Non-Narcotic Analgesic category from Schedule 3 to Schedule 5 (prescription only) excluding the Meprobamate products for each Company was determined. See Table 3

The % Market Share in the OTC Non-Narcotic Analgesic category from Schedule 1 to Schedule 2 for each Company was determined. See Table 4

The % Market Share in the whole Non-Narcotic Analgesic category from Schedule 1 to Schedule 5 excluding the Meprobamate products for each Company was determined. See Table 5

Calculation for Economic Impact per Pharmaceutical Company.

A= [Quantity of Meprobamate containing analgesic dosage units (capsules/tablets) for 2001 for each Company x Company average price for a meprobamate containing analgesic in 2001.]

B_1= [% Market Share of the prescription Non-Narcotic Analgesic Market (S_3 to S_5) for each Company x Total quantity of Meprobamate containing analgesic dosage units (capsules/tablets) for the year 2001 x the Company average price for a Non-Narcotic Analgesic (S_3 to S_5) in the year 2001.]

$C_1 = B_1 - A$

C_1 is the Rand value gain/loss for each Company on switching from a Meprobamate containing analgesic to another prescription Non-Narcotic Analgesic (S3 to S5). See Table 3

B_2= [% Market Share of the OTC Non-Narcotic Analgesic Market (S_1 to S_2) for each Company x Total quantity of Meprobamate containing analgesic dosage units (capsules/tablets) for the year 2001 x the Company average price for a Non-Narcotic Analgesic (S_1 to S_2) in the year 2001.]

$C_2 = B_2 - A$

C_2 is the Rand value gain/loss for each Company on switching from a Meprobamate containing analgesic to another OTC Non-Narcotic Analgesic (S1 to S2). See Table 4

B_3= [% Market Share of the whole Non-Narcotic Analgesic Market (S1 to S5) for each Company x Total quantity of Meprobamate containing analgesic dosage units (caps/tabs) for the year 2001 x the Company average price for a Non-Narcotic Analgesic (S1 to S5) in the year 2001.]

$C_3 = B_3 - A$

C_3 is the Rand value gain/loss for each Company on switching from a Meprobamate containing analgesic to another Non-Narcotic Analgesic (S_1 to S_5). See Table 5

Table 3: Economic impact of switch from Meprobamate products to prescription-only Non-Narcotic Analgesics

	Meprobamate containing analgesics			Non-Meprobamate - non-narcotic analgesics - prescription only (S3-S5)					
Company	Rand value	Dosage units	Company average price	Rand value	Dosage units	Company average price	Market share	New replacement dosage units	Rand value gain on switch
Aspen	21,597,000	88,948,000	0.24	26,994,000	17,692,000	1.53	13.6%	23,075,055	+13,610,327
Brovar	101,000	400,000	0.25	0	0	0.00	0.0%	0	-101,000
Xeragen	2,000	8,000	0.25	0	0	0.00	0.0%	0	-2,000
Crown Laboratories	67,000	97,500	0.69	0	0	0.00	0.0%	0	-67,000
Ranbaxy	183,000	850,000	0.22	0	0	0.00	0.0%	0	-183,000
A I Healthcare	49,070,000	60,018,000	0.82	177,420,000	93,026,000	1.91	71.4%	121,330,548	+182,332,681
Rolab	345,000	502,000	0.69	1,917,000	2,490,000	0.77	1.9%	3,247,620	+2,155,276
Cipla-Medpro	1,141,000	3,170,000	0.36	0	0	0.00	0.0%	0	-1,141,000
Alliance	3,532,000	15,418,000	0.23	0	0	0.00	0.0%	0	-3,532,000
Ormed	207,000	200,000	1.04	0	0	0.00	0.0%	0	-207,000
Xixia Pharmaceuticals	103,000	216,000	0.48	0	0	0.00	0.0%	0	-103,000
PD Pharm	0	0	0.00	0	0	0.00	0.0%	0	0
Janssen	0	0	0.00	6,147,000	2,854,000	2.15	2.2%	3,722,372	+8,017,316
Roche	0	0	0.00	1,625,000	382,600	4.25	0.3%	499,012	+2,119,430
Parke Med	0	0	0.00	1,064,000	2,136,000	0.50	1.6%	2,785,910	+1,387,738
Hexal Pharmaceuticals	0	0	0.00	2,864,000	2,188,000	1.31	1.7%	2,853,732	+3,735,415
Be-tabs Pharmaceuticals	0	0	0.00	1,766,000	8,870,000	0.20	6.8%	11,568,830	+2,303,332
Aventis	0	0	0.00	1,070,000	570,000	1.88	0.4%	743,431	+1,395,563
Merck Sharpe Dohme	0	0	0.00	3,000	760	3.95	0.0%	991	+3,913
Reckitt Benckiser	0	0	0.00	0	0	0.00	0.0%	0	0
Glaxosmithkline	0	0	0.00	0	0	0.00	0.0%	0	0
Pharmachoice Hic	0	0	0.00	0	0	0.00	0.0%	0	0
Byk Madaus	0	0	0.00	0	0	0.00	0.0%	0	0
Whitehall	0	0	0.00	0	0	0.00	0.0%	0	0
3M Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Bayer	0	0	0.00	0	0	0.00	0.0%	0	0
Caps Pharmaceutica	0	0	0.00	0	0	0.00	0.0%	0	0
Merck Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Karoo Apteek	0	0	0.00	0	0	0.00	0.0%	0	0
National Druggists	0	0	0.00	0	0	0.00	0.0%	0	0
Link Own Brand	0	0	0.00	0	0	0.00	0.0%	0	0
Kemtrade	0	0	0.00	0	0	0.00	0.0%	0	0
Beige Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Total	76,348,000	169,827,500	0.45	220,870,000	130,209,360	1.70	100.0%	169,827,500	+211,724,992

Table 4: Economic impact of switch from Meprobamate products to OTC Non-Narcotic Analgesics

	Meprobamate containing analgesics			Non-Meprobamate - non-narcotic - over-the-counter (S1-S2)					
Company	Rand value	Dosage units	Company average price	Rand value	Dosage units	Company average price	Market share	New replacement dosage units	Rand value gain on switch
Aspen	21,597,000	88,948,000	0.24	35,090,000	82,088,200	0.43	12.1%	20,592,366	-12,794,442
Brovar	101,000	400,000	0.25	0	0	0.00	0.0%	0	-101,000
Xeragen	2,000	8,000	0.25	571,000	856,400	0.67	0.1%	214,834	+141,239
Crown Laboratories	67,000	97,500	0.69	0	0	0.00	0.0%	0	-67,000
Ranbaxy	183,000	850,000	0.22	0	0	0.00	0.0%	0	-183,000
A I Healthcare	49,070,000	50,018,000	0.82	239,050,000	386,154,600	0.62	57.0%	96,869,424	+10,897,267
Rolab	345,000	502,000	0.69	12,000	78,000	0.15	0.0%	19,567	-341,990
Cipla-Medpro	1,141,000	3,170,000	0.36	0	0	0.00	0.0%	0	-1,141,000
Alliance	3,532,000	15,418,000	0.23	0	0	0.00	0.0%	0	-3,532,000
Ormed	207,000	200,000	1.04	0	0	0.00	0.0%	0	-207,000
Xixia Pharmaceuticals	103,000	216,000	0.48	0	0	0.00	0.0%	0	-103,000
PD Pharm	0	0	0.00	0	0	0.00	0.0%	0	0
Janssen	0	0	0.00	1,536,000	1,966,800	0.78	0.3%	493,385	+385,316
Roche	0	0	0.00	0	0	0.00	0.0%	0	0
Parke Med	0	0	0.00	0	0	0.00	0.0%	0	0
Hexal Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Be-tabs Pharmaceuticals	0	0	0.00	4,397,000	98,115,000	0.04	14.5%	24,612,794	+1,103,016
Aventis	0	0	0.00	5,286,000	17,843,000	0.30	2.6%	4,476,034	+1,326,028
Merck Sharpe Dohme	0	0	0.00	0	0	0.00	0.0%	0	0
Reckitt Benckiser	0	0	0.00	27,067,000	58,393,400	0.46	8.6%	14,648,369	+6,789,935
Glaxosmithkline	0	0	0.00	1,413,000	4,031,600	0.35	0.6%	1,011,353	+354,460
Pharmachoice Hic	0	0	0.00	2,029,000	5,952,000	0.34	0.9%	1,493,098	+508,988
Byk Madaus	0	0	0.00	175,000	1,488,000	0.12	0.2%	373,275	+43,900
Whitehall	0	0	0.00	706,000	2,964,000	0.24	0.4%	743,539	+177,105
3M Pharmaceuticals	0	0	0.00	553,000	909,600	0.61	0.1%	228,179	+138,724
Bayer	0	0	0.00	538,000	2,509,000	0.21	0.4%	629,399	+134,961
Caps Pharmaceutica	0	0	0.00	490,000	10,900,000	0.04	1.6%	2,734,337	+122,920
Merck Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Karoo Apteek	0	0	0.00	115,000	526,800	0.22	0.1%	132,151	+28,849
National Druggists	0	0	0.00	98,000	1,105,000	0.09	0.2%	277,197	+24,584
Link Own Brand	0	0	0.00	80,000	1,058,000	0.08	0.2%	265,406	+20,069
Kemtrade	0	0	0.00	37,000	36,000	1.03	0.0%	9,031	+9,282
Beige Pharmaceuticals	0	0	0.00	3,000	15,000	0.20	0.0%	3,763	+753
Total	76,348,000	169,827,500	0.45	319,246,000	676,990,400	0.47	100.0%	169,827,500	+3,736,961

Table 5: Economic impact of switch from Meprobamate products to all Non-Narcotic Analgesics

	Meprobamate containing analgesics			Non-Meprobamate - all non-narcotic analgesics (S1-S5)					
Company	Rand value	Dosage units	Company average price	Rand value	Dosage units	Company average price	Market share	New replacement dosage units	Rand value gain on switch
Aspen	21,597,000	88,948,000	0.24	62,084,000	99,780,200	0.62	12.4%	20,992,848	-8,535,090
Brovar	101,000	400,000	0.25	0	0	0.00	0.0%	0	-101,000
Xeragen	2,000	8,000	0.25	571,000	856,400	0.67	0.1%	180,179	+118,133
Crown Laboratories	67,000	97,500	0.69	0	0	0.00	0.0%	0	-67,000
Ranbaxy	183,000	850,000	0.22	0	0	0.00	0.0%	0	-183,000
A I Healthcare	49,070,000	60,018,000	0.82	416,470,000	479,180,600	0.87	59.4%	100,815,247	+38,551,506
Rolab	345,000	502,000	0.69	1,929,000	2,568,000	0.75	0.3%	540,284	+60,844
Cipla-Medpro	1,141,000	3,170,000	0.36	0	0	0.00	0.0%	0	-1,141,000
Alliance	3,532,000	15,418,000	0.23	0	0	0.00	0.0%	0	-3,532,000
Ormed	207,000	200,000	1.04	0	0	0.00	0.0%	0	-207,000
Xixia Pharmaceuticals	103,000	216,000	0.48	0	0	0.00	0.0%	0	-103,000
PD Pharm	0	0	0.00	0	0	0.00	0.0%	0	0
Janssen	0	0	0.00	7,683,000	4,820,800	1.59	0.6%	1,014,253	+1,616,433
Roche	0	0	0.00	1,625,000	382,600	4.25	0.0%	80,496	+341,885
Parke Med	0	0	0.00	1,064,000	2,136,000	0.50	0.3%	449,395	+223,856
Hexal Pharmaceuticals	0	0	0.00	2,864,000	2,188,000	1.31	0.3%	460,335	+602,560
Be-tabs Pharmaceuticals	0	0	0.00	6,163,000	106,985,000	0.06	13.3%	22,508,673	+1,296,639
Aventis	0	0	0.00	6,356,000	18,413,000	0.35	2.3%	3,873,928	+1,337,245
Merck Sharpe Dohme	0	0	0.00	3,000	760	3.95	0.0%	160	+631
Reckitt Benckiser	0	0	0.00	27,067,000	58,393,400	0.46	7.2%	12,285,441	+5,694,651
Glaxosmithkline	0	0	0.00	1,413,000	4,031,600	0.35	0.5%	848,212	+297,282
Pharmachoice Hic	0	0	0.00	2,029,000	5,952,000	0.34	0.7%	1,252,247	+426,883
Byk Madaus	0	0	0.00	175,000	1,488,000	0.12	0.2%	313,062	+36,818
Whitehall	0	0	0.00	706,000	2,964,000	0.24	0.4%	623,599	+148,536
3M Pharmaceuticals	0	0	0.00	553,000	909,600	0.61	0.1%	191,372	+116,346
Bayer	0	0	0.00	538,000	2,509,000	0.21	0.3%	527,871	+113,190
Caps Pharmaceutica	0	0	0.00	490,000	10,900,000	0.04	1.4%	2,293,261	+103,092
Merck Pharmaceuticals	0	0	0.00	0	0	0.00	0.0%	0	0
Karoo Apteek	0	0	0.00	115,000	526,800	0.22	0.1%	110,834	+24,195
National Druggists	0	0	0.00	98,000	1,105,000	0.09	0.1%	232,482	+20,618
Link Own Brand	0	0	0.00	80,000	1,058,000	0.08	0.1%	222,594	+16,831
Kemtrade	0	0	0.00	37,000	36,000	1.03	0.0%	7,574	+7,784
Beige Pharmaceuticals	0	0	0.00	3,000	15,000	0.20	0.0%	3,156	+631
Total	76,348,000	169,827,500	0.45	540,116,000	807,199,760	0.67	100.0%	169,827,500	+37,287,502

5. Discussion

5.1 Clinical Aspect

In discussion of research Question 1:

- Is there evidence that Meprobamate contributes meaningfully to the therapeutic effect of the analgesic combination?

The investigation of pain is difficult but of great clinical importance. The relief of pain differs between patients relative to their perception and experience of pain making a study of this nature more difficult to objectively analyze compared to an evaluation of an antibiotic for an acute infection.

The design of trial to objectively assess pain relief of multi-component analgesic requires the following elements:

A placebo,

The multicomponent

An appropriate single component analgesic

The individual components of the multi-component analgesic

A validated measuring instrument (e.g. an analogue pain scale or other suitable instrument.)[24]

Based on the analysis of the clinical trials according to the ICH guidelines, no evidence could be found to prove that meprobamate in combination analgesics provides any therapeutic benefit. Although the findings in the Stopayne® trials suggested that there was analgesic benefit. The design of the trials did not include a placebo or another drug comparator. The analgesic effect reported, could be due to a placebo effect or it could be due to the combination of paracetamol and codeine in the Stopayne® product. Beaver,WT (1981)[39] reported that the additive effect of the combination of paracetamol and codeine produces greater analgesia than twice the dose of either drug given alone. Further, clinical proof for the efficacy of meprobamate as a selective antianxiety agent in human beings is lacking.[22]

In South Africa, meprobamate in combination with aspirin and ethoheptazine, Equagesic®,has no recorded sales since 1998.[4,5,6,7,8,9,10,11,12,13]

Laska *et al* (1983)[38] reported that the addition of caffeine to paracetamol significantly reduced the time to analgesic onset when compared with paracetamol alone. It was also been suggested that caffeine may elevate the mood, promoting a feeling of "well-being".

In discussion of research Question 2:

- Does the risk/benefit ratio of the meprobamate combination warrant the continual marketing of these products?

Meprobamate is preferred to the benzodiazepines by subjects with a history of drug abuse. After long-term medication, abrupt discontinuation evokes a withdrawal syndrome usually characterized by anxiety, insomnia, tremors and frequently hallucinations: generalized seizures occur in about 10% of cases.[22]

Reeves *et al* (1999)[23] reported that the abuse of meprobamate has continued despite a substantial decrease in the clinical use of the drug. *Carisoprodol (*Soma*)*, a skeletal muscle relaxant whose active metabolite is meprobamate, has become a popular "street drug".

Most of the meprobamate containing analgesics on the South African market contain meprobamate in a dosage strength of 150mg per capsule or tablet. See Table 1. The usual anxiolytic dose is 400mg by mouth 3 to 4 times a day up to a maximum of 2,4g daily. In elderly patients, no more than half the usual adult dose has been suggested.[32]

Based on the analysis of the clinical trials no serious side effects were reported other than drowsiness and sedation. Most patients took the trial medication for a period of 2 or 3 days and none for longer than 7 days. This was not a sufficient time period to adequately assess adverse drug reactions and side effects and the possible addiction or withdrawal symptoms that could have presented when taking a dosage unit containing 150mg of meprobamate. After long–term medication, abrupt discontinuation evokes a withdrawal syndrome characterized by anxiety, insomnia, tremors and frequently hallucinations[17]. According to other research meprobamate used alone or in combination with an analgesic, in the management of muscle spasm and painful musculoskeletal disorders is no longer considered appropriate.[41] Reeves *et al,*(1999)[23] who studied the abuse potential and physician unawareness of carisoprodol (Soma) reported that carisoprodol whose active metabolite is meprobamate has abuse potential and has become a popular "street drug".

There is no evidence to prove the benefit of meprobamate in combination analgesics and there is evidence that meprobamate evokes a withdrawal syndrome after long-term use.

5.2 Economic Aspect

In discussion of Question 3:

- What is the trend in sales of these meprobamate-containing analgesics and what is the financial % market share relative to the whole non-narcotic analgesic market and is the trend in sales increasing, decreasing or remaining stable.

The trend in the sales of these meprobamate containing products decreased for one year from 1992 to 1993 then increased for 5 years, from 1993 to 1997 then decreased again for 2 years from 1998 to 1999.Sales then increased again in the year 2000 and further increased in 2001, disproportionately to the trend increases of 1993 to 1997. See Figure 3

The % market share of meprobamate containing analgesics in 1992 was 13,9 % and in 2001 10,7%. See Figure 6

The total sum of dosage units containing meprobamate sold in 1992 was 109,076,048, (population adjusted) which decreased to 96,494,299 in 1993. From 1993 up to 2000 there was an increasing quantity of meprobamate containing products sold each year on reaching 124,135,303 dosage units by 2000. In 2001 there was a large increase in dosage units sold numbering 169,827,500.This trend in increasing sales between 1993 and 2001 can only be explained either by a vigorous marketing campaign for these products or by an increase in their abuse.

The Rand Value of the meprobamate containing products in relation to the whole non-narcotic analgesic market showed that in 2000 and 2001 there was an increase in the trend unrelated to the downward trend shown between 1992 to 1999. See Figure 6

The trend in the % market share showed a decrease for 3 years from 1992 to 1995, which then picked up in the year 1996 and then decreased for another 3 years from 1996 to 1999.The last 2 years showed that the trend in the % market share began increasing again from 1999 to 2001.

In 2001 the Rand value of all the non-narcotic analgesics amounted to R712, 291,000 and the Meprobamate containing portion was R76, 348,000 i.e. 10,7%. The number of dosage units of prescription only non-narcotic analgesics (S_3 to S_5) sold in 2001 not containing Meprobamate was 130, 209,360 which generated a revenue of R220, 870,000. The number of Meprobamate dosage units sold in the same year were 169,827,500.This was 39,618,140 capsules/tablets more than the number of the other prescription only Non –narcotic analgesic dosage units, but generated a revenue of R76, 348,500 as opposed to R220, 870,000. This greater volume in sales of the meprobamate dosage units that generated less revenue than the other prescription non-narcotic analgesics was due to the pricing structure of the different products.

The analysis of the IMS data showed that in 2001 there were a total of 300,036,860 capsules/ tablets sold in the prescription non-narcotic analgesic category, i.e., from Schedule 3 to Schedule 5. See Table 3.

Of this amount of prescription dosage units sold, 169,827,500 were for meprobamate containing products, which represents 56,6% of the whole S_3 to S_5 Non-narcotic analgesic market. See Table 3.This means that more than half of all the prescription only non-narcotic analgesics sold were for meprobamate containing products, which are in the Schedule 5 category.

Meprobamate containing analgesics which are all in Schedule 5 category and cannot be sold on a patient's request. There has to be a valid doctor's prescription before it can be dispensed. Analysis of the IMS data has shown more dosage units of meprobamate containing analgesics were sold than the other prescription only Non-narcotic analgesic dosage units. Two possible reasons could account for this. One reason could be that the doctor is considerate of the cost to the patient as the meprobamate containing products are on average "cheaper" than the other prescription only Non- narcotic analgesics. The other reason could be that the patients are requesting these products from their doctors and the doctors are unaware of possible patient abuse.

In discussion of research Question 4:

- What is the likely economic implication of the withdrawal of meprobamate containing combination analgesics from the market?

If the Medicines Control Council of South Africa were to withdraw the meprobamate containing products then certain pharmaceutical companies would gain financially while others would loose depending on whether patients switched to another prescription only non narcotic analgesic, or an over –the – counter substitute or both and depending upon each pharmaceutical company's market share in each respective category (See Tables 3,4 and Table 5, based on the research of the Total Private Market). Meprobamate containing products are not included in the Essential Drug List of 1998.[40]

Table 3: Discussion

This table shows what the likely economic impact on certain pharmaceutical companies would be, if patients were to take instead of a meprobamate containing analgesic another non-narcotic analgesic within the scheduling category of S3 to S5 that like meprobamate requires a presciption.

The assessment is on the likely economic gain/loss to the Company assuming the patient is switched on a one to one basis i.e. for example that for every X number of meprobamate containing capsules/tablets the patient is prescribed they will be prescribed X number of another non-narcotic analgesic.

The far left hand column shows the Companies that have products containing meprobamate and or products that fall in to the prescription only non-narcotic analgesic category of S3 to S5.

The second major column relates to Meprobamate containing analgesics and has 3 sub-columns. The first sub-column on the far left of this column shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

The third major column relates to all other Non-narcotic analgesics that require a prescription, fall within the scheduling category of 3 to 5 and do not include meprobamate. The first sub-column on the far left of this column shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

Sub-column 4 shows the % market share of each company for all prescription only non-narcotic analgesics (S3 to S5). This is worked out by taking the total number of dosage units for each Company and dividing it by the accumulative total number of all the dosage units and then multiplying by a 100 to convert to %.

Sub-column 5 shows the new replacement dosage units. Assuming as said earlier that meprobamate products are switched on a one to one basis then whatever % of the non-narcotic analgesic market a company captured they would equally capture that of the meprobamate products. This is worked out by taking the % market share of the non-narcotic analgesics and multiplying it by the accumulative total number of meprobamate dosage units.

Sub-column 6 shows the Rand value loss/gain on this switching process. This is worked out by subtracting the [(total number of meprobamate dosages units X company average price of the meprobamate units) from the (new replacement units of the non-narcotic analgesics X company average price of the non- narcotic analgesics units)]

Of particular mention would be the effect to A I Healthcare (Adcock Ingrams) and Aspen who together market 87,7% of all the Meprobamate containing analgesics.

Aspen captures 52,4% of the Meprobamate combination analgesic market and 13,6% of the prescription only Non-narcotic analgesic (S_3 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then Aspen would stand to gain R13, 6 million by this switch.

A I Healthcare captures 35,3% of the Meprobamate containing market and 71,4% of the prescription only non-narcotic analgesic (S_3 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then A I Healthcare would stand to gain R182, 3 million by this switch.

Janssen captures 0.0% of the Meprobamate containing market and 2,2% of the prescription only non-narcotic analgesic (S_3 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then Janssen would stand to gain R8,01 million by this switch.

Table 4: Discussion

This table shows what the likely economic impact on certain pharmaceutical companies would be, if patients were to take instead of a meprobamate containing analgesic another non-narcotic over–the-counter analgesic within the scheduling category of S1 to S2.

The assessment is on the likely economic gain/loss to the Company assuming the patient is switched on a one to one basis i.e. for example that for every X number of meprobamate containing capsules/tablets the patient is prescribed they will be prescribed X number of another non-narcotic over-the-counter analgesic.

The far left hand column shows the Companies that have products containing meprobamate and or products that fall in to the non-narcotic over-the-counter analgesic category of S1 to S2.

The second major column relates to Meprobamate containing analgesics and has 3 sub-columns. The first sub-column on the far left of this column shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

The third major column relates to all other Non-narcotic over-the-counter analgesics that do not require a prescription, fall within the scheduling category of 1 to 2 and do not include meprobamate. The first sub-column on the far left shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

Sub-column 4 shows the % market share of each company for all non-narcotic over-the-counter analgesics. This is worked out by taking the total number of dosage units for each Company and dividing it by the accumulative total number of all the dosage units and then multiplying by a 100 to convert to %.

Sub-column 5 shows the new replacement dosage units. Assuming as said earlier that meprobamate products are switched on a one to one basis then whatever % of the non-narcotic over-the-counter analgesic market a company captured they would equally capture that of the meprobamate products. This is worked out by taking the %market share of the non-narcotic analgesics and multiplying it by the accumulative total number of meprobamate dosage units.

Sub-column 6 shows the Rand value loss/gain on this switching process. This is worked out by subtracting the [(total number of meprobamate dosages units X company average price of the meprobamate units) from the (new replacement units of the non-narcotic over-the-counter analgesics X company average price of the non- narcotic over-the-counter analgesic units)]

Aspen captures 52,4% of the Meprobamate combination analgesic market and 12,1% of the Non-narcotic over-the-counter analgesic (S_1 to S_2) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic that could be bought over–the-counter then Aspen would stand to loose R12,8 million by this switch.

A.I Healthcare captures 35,3% of the Meprobamate combination analgesic market and 57,0% of the Non-narcotic over-the-counter analgesic (S_1 to S_2) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic that could be bought over–the-counter then A.I.Healthcare would stand to gain R10,9 million by this switch.

Janssen captures 0.0% of the Meprobamate containing market and 0,3% of the prescription only non-narcotic over-the-counter analgesic (S_1 to S_2) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then Janssen would stand to gain R385,316.

Table 5: Discussion

This table shows what the likely economic impact on certain pharmaceutical companies would be, if patients were to take instead of a meprobamate containing analgesic another non-narcotic analgesic within the scheduling category of S1 to S5.

The assessment is on the likely economic gain/loss to the Company assuming the patient is switched on a one to one basis i.e. for example that for every X number of meprobamate containing capsules/tablets the patient is prescribed they will be prescribed X number of another non-narcotic analgesic.

The far left hand column shows the Companies that have products containing meprobamate and or products that fall in to the non-narcotic analgesic category of S1 to S5.

The second major column relates to Meprobamate containing analgesics and has 3 sub-columns. The first sub-column on the far left of this column shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

The third major column relates to all other Non-narcotic analgesics that fall within the scheduling category of 1 to 5 and do not include meprobamate. The first sub-column on the far left shows the total Rand Value for all the capsules/tablets of each company. The second sub-column shows how many dosage units i.e. capsules/tablets each company sold in the year 2001. By dividing the Rand Value by the total number of dosage units the average company price per capsule/tablet is worked out. This is shown in sub-column 3.

Sub-column 4 shows the % market share of each company for all non-narcotic analgesics from S1 to S5. This is worked out by taking the total number of dosage units for each Company and dividing it by the accumulative total number of all the dosage units and then multiplying by a 100 to convert to %.

Sub-column 5 shows the new replacement dosage units. Assuming as said earlier that meprobamate products are switched on a one to one basis then whatever % of the non-narcotic analgesic market a company captured they would equally capture that of the meprobamate products. This is worked out by taking the %market share of the non-narcotic analgesics and multiplying it by the accumulative total number of meprobamate dosage units.

Sub-column 6 shows the Rand value loss/gain on this switching process. This is worked out by subtracting the [(total number of meprobamate dosages units X company average price of the meprobamate units) from the (new replacement units of the non-narcotic analgesics X company average price of the non-narcotic analgesic units)]

Aspen captures 52,4% of the Meprobamate combination analgesic market and 12,4% of the Non-narcotic analgesic (S_1 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring either a presciption or bought over-the-counter then Aspen would stand to loose R8,5 million by this switch.

A.I Healthcare captures 35,3% of the Meprobamate combination analgesic market and 59,4% of the Non-narcotic analgesic (S_1 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring either a presciption or bought over–the-counter then A.I.Healthcare would stand to gain R38,5 million by this switch.

Janssen captures 0.0% of the Meprobamate containing market and 0,6% of the Non-narcotic analgesic (S_1 to S_5) market. In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then Janssen would stand to gain R1,61 million.

In discussion of research Question 5:

- Should meprobamate in combination analgesic preparations continue to be allowed to remain on the South African Market?

In the USA multi-ingredient preparations with Meprobamate are only in combination with aspirin and sold under the trade names of Deprol; Epromate; Equagesic; Equazine M; Micrainin; PMB.

In the UK multi-ingredient preparations with Meprobamate were only in combination with aspirin and sold under the trade names of Equagesic; Paxidal. As of 31st March 2002 these products were withdrawn.

South Africa is the only country in the world that markets meprobamate in combination with paracetamol, codeine and caffeine. As discussed in research questions 1 and 2, there was no evidence in all the clinical studies to suggest there was any therapeutic benefit. What is also known from research on as recently as 1999 is that Reeves *et al* (1999)[23] reported that the abuse of meprobamate has continued despite a substantial decrease in the clinical use of the drug. *Carisoprodol (*Soma*)*, a skeletal muscle relaxant whose active metabolite is meprobamate, has become a popular "street drug".

There is no evidence to suggest that it is beneficial to the public for meprobamate in combination analgesic preparations to continue to be allowed to remain on the South African Market.

Analysis of the IMS marketing and sales data shows that the overall economic impact of such a product withdrawal on the Pharmaceutical Industry would be positive rather than detrimental.

6. Conclusions and Recommendations

In conclusion to research Question 1:

- Is there evidence that Meprobamate contributes meaningfully to the therapeutic effect of the analgesic combination?

Of the 10 clinical studies on meprobamate in combination analgesics, only three studies included a placebo and another drug comparator. These studies studied the effect of meprobamate in combination with aspirin, and meprobamate in combination with aspirin and ethoheptazine. Since 1998 in South Africa, meprobamate in combination with aspirin is no longer marketed making such trials no longer relevant.

The other 7 trials studied the effect of meprobamate in combination with paracetamol, codeine and caffeine (Stopayne®) but failed to include a placebo or drug comparator, containing paracetamol, codeine and caffeine.

There is no evidence to suggest in any of the trials that studied the efficacy of Stopayne®, that meprobamate contributes meaningfully to the therapeutic effect.

In conclusion to research Question 2:

- Does the risk/benefit ratio of the meprobamate combination warrant the continual marketing of these products?

In all the clinical studies, none reported any serious side effects other than drowsiness and sedation. None of the patients were ever assessed for a period longer than 7 days so the abuse potential of meprobamate was not adequately explored within the clinical trials.

Other research has reported that after long-term medication, abrupt discontinuation evokes a withdrawal syndrome characterized by anxiety, insomnia, tremors and frequently hallucinations.[17]

It is recommended that all products on the South African market containing meprobamate in combination analgesics be withdrawn as the risk/benefit ratio does not warrant the continual marketing of these products.

In conclusion to research Question 3

- What is the trend in sales of these meprobamate-containing analgesics and what is the financial % market share relative to the whole non-narcotic analgesic market and is the trend in sales increasing, decreasing or remaining stable.

The overall trend in the sales of these meprobamate products from 1992 to 2001 has been an increase. The overall trend in the sales of all non-narcotic analgesic products has also seen an increase from 1992 to 2001. The % market share of the meprobamate products relative to all the non-narcotic analgesics has been decreasing from 1992 until 1999 because the increased sales each year of the other non-narcotic analgesics was still greater than the increased sales of the meprobamate products. A reverse of the trend was seen in 2000 and 2001 whereby the increase in meprobamate sales was much greater than the increase the overall non-narcotic sales. This indicates that from 2000 the trend is again increasing.

South Africa is the only country in the world that sells meprobamate in combination with paracetamol and codeine and caffeine. No other Medicine Regulatory Authority has granted a license for such a product combination. Research has shown that in South Africa more than half of all the prescription only Non-Narcotic Analgesics from Schedule 3 to Schedule 5 sold (56,6%), were for these meprobamate-containing products, which are not registered in any other country.

In conclusion to research Question 4:

- What is the likely economic implication of the withdrawal of meprobamate containing combination analgesics from the market?

Some pharmaceutical companies would suffer a financial loss while others would gain by the withdrawal of Meprobamate containing combination analgesics. The gain or loss would depend on the scheduling category of the substitute single/multi component analgesic to which the patient was switched.

In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then Aspen would stand to gain R13, 6 million by this switch.

In the likely event that all patients on a meprobamate containing analgesic were given another analgesic that could only be bought over–the–counter then Aspen would stand to loose R12, 8 million by this switch.

In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring either a prescription or bought over – the -counter then Aspen would stand to loose R8, 5 million by this switch.

In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring a prescription then A I Healthcare would stand to gain R182, 3 million by this switch.

In the likely event that all patients on a meprobamate containing analgesic were given another over–the-counter analgesic then A I Healthcare would stand to gain R10, 9 million by this switch.

In the likely event that all patients on a meprobamate containing analgesic were given another analgesic requiring either a prescription or an over-the-counter analgesic then A I Healthcare would stand to gain R38, 5 million by this switch.

In conclusion to research question 5:

- Should meprobamate in combination analgesic preparations continue to be allowed to remain on the South African Market?

South Africa is the only country to have available on its market a combination such as meprobamate in conjunction with caffeine, codeine and paracetamol. There was a greater number of analgesic dosage units sold in 2001 containing meprobamate than the sum of all the other prescription only non-narcotic analgesics. Of the whole prescription only non-narcotic analgesic market from Schedule 3 to Schedule 5, 56,6% were the meprobamate containing products.

The clinical trials of Meprobamate did not show any therapeutic benefit. It has been reported that Carisoprodol whose active metabolite is Meprobamate has abuse potential and has become a popular street drug.

The recommendation from this study report is that Meprobamate in combination with other analgesics has no therapeutic benefit. In addition it has a potential for addiction and abuse, which has not been adequately investigated. It is recommended that all Meprobamate containing combination analgesics be withdrawn.

If meprobamate products are not withdrawn from the market then post marketing surveillance of the efficacy and safety of these combination analgesics should be under taken.

The Companies should be obliged to take more stringent adverse event reporting.

In terms of Act 90 when companies are required to re-register their products, double blind randomized studies should be under taken.

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APPENDICES

Appendix A: Medicine Control Council circular (11/98)

GW 12/40

MEDISYNEBEHEERRAAD

Republiek van Suid-Afrika

MEDICINES CONTROL COUNCIL

Republic of South Africa

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DEPARTEMENT VAN GESONDHEID
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THE REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
PRIVATE BAG X828
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0001
HALLMARK BUILDING

Navrae - Inquiries: Mrs Sophie Fourie
Verwysing - Reference: 26/6/2/1 Meprobamate

CIRCULAR 11 / 98

TO ALL APPLICANTS

Dear Sir/Madam

MEDICINES CONTAINING MEPROBAMATE IN COMBINATION WITH ANALGESICS

The Medicines Control Council has resolved to reassess the inclusion of meprobamate in combination analgesics.

Interested parties are invited to comment on the scientific rationale behind the inclusion of meprobamate in analgesic preparations. This should include evidence that meprobamate contributes meaningfully to the therapeutic effect of the analgesic combination. In addition, the risk - benefit balance of the meprobamate combination should be adequately addressed.

Submissions should be received at this office within 90 calendar days of the date appearing on this letter.

Yours Faithfully

REGISTRAR OF MEDICINES

5/11/98

Appendix B: Detailed summary of Clinical Trials

Trial 1: (1973)

Gilbert MM, Koepke HH. Relief of musculo-skeletal and associated psychopathological symptoms with meprobamate and aspirin: a controlled study. Current Therapeutic Research 1973; 15 (11): 820.

Type of Study:

Double – Blind study to compare the clinical response to a combination of meprobamate and aspirin, to aspirin and meprobamate alone and to a placebo in the treatment of patients suffering from moderate to severe musculo-skeletal symptoms associated with anxiety.

Method:

118 men, women and adolescents with mean age of 40 seen as outpatients in a neuropsychiatric practice in Miami, Florida.

Most patients' physical symptoms (pain, spasm, cramps) were the consequences of automobile accidents and were accompanied by emotional stress of a situational nature (anxiety, tension and apprehension).

Patients were assigned at random.

Dose:

All medication administered was of uniform size and appearance.

Each tablet contained 325mg aspirin, 200mg meprobamate, 325mg aspirin plus 200mg meprobamate, or a placebo.

Patients were instructed to take 2 tablets three times a day for three days.

All patients were rated again on the second and third day.

Results:

Of 118 patients studied, six did not complete the study. One assigned to the combined medication (Did not return after the first visit). Two assigned to the meprobamate alone (Dropped out because of side effects, stomach upset, gastrointestinal burning). Three assigned to the placebo. (Two discontinued because they "Felt worse", one misunderstood directions and took only one dose.).

Of the remaining 112 patients who finished the study. For the results see table for side-effects and relief of pain.

Table 6: Side effects - Trial 1

Variable	Combination N=29			Aspirin N=29			Meprobamate N=28			Placebo N=26		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Drowsiness	10			5		1	5		1	1		
Upset Stomach	1											
Dizziness							1					
G-I Burning									1			

Relief of Pain.

On a scale of 1 to 4 where the lowest number is indicative of the greatest relief of pain.

Table 7: Relief of pain - Trial 1

	Combination N=29	Aspirin N=29	Meprobamate N=28	Placebo N=26
Mean	1.828	2.310	2.643	3.308
SD	0.805	0.891	1.162	1.087

The resultant data were tested for main drug effects and drug interaction by 2x2 factorial analysis. Aspirin significantly relieved pain but did not effect the emotional symptoms. Meprobamate on its own was significantly effective against emotional stress and reduced pain to a lesser degree. The combination of aspirin and meprobamate demonstrated the greatest relief of both physical and psychological symptoms.

Trial 2: (1974)

Schriener JJ, Richards DJ. Treatment of musculoskeletal pain and associated anxiety with an ethoheptazine- aspirin-meprobamate combination (Equagesic): a controlled study. Curr Ther Res 1974; 16(9): 928-935.

Type of Study:

A Double – Blind crossover study to compare the efficacy of a combination containing ethoheptazine75mg,aspirin 250mg,and meprobamate 150mg; compared to a combination containing aspirin 250mg and ethoheptazine 75mg; compared to meprobamate 150mg compared to a placebo in the treatment of the symptoms of pain and anxiety on the basis of evidence of acute traumatic lumbar sprain with attendant muscle spasm.

Method:

99 men, women between the ages of 22 and 62 seen as out-patients in an orthopaedic clinic.

Patients were selected on the basis of evidence of acute traumatic lumbar sprain with attendant muscle spasm, limited range of motion, pain and anxiety as determined by a pre-study physical examination.

Patients were assigned to treatments according to a previously randomized allocation schedule following a six hour respite from analgesic and tranquilizer medication.

Dose:

Each patient received two tablets of the placebo as the first dose. The three other agents of uniform size and appearance, were given in a dose of two tablets per patient in cross over fashion representing all possible permutations of therapy sequence as follows:

Table 8: Treatment order - Trial 2

Treatment Order	1 N=16	2 N=14	3 N=18	4 N=17	5 N=17	6 N=15
Dose No.1	P	P	P	P	P	P
Dose No.2	A	A	C	C	B	B
Dose No.3	B	C	B	A	A	C
Dose No.4	C	B	A	B	C	A

A-aspirin 250mg plus ethoheptazine 75mg

B-meprobamate 150mg

C-meprobamate 150mg, aspirin 250mg, ethoheptazine 75mg

P-placebo

Results:

The effectiveness of medication for both symptoms of pain and anxiety was rated by the patient as *none* (N), *partial* (P), *complete* (C) at one, two and three hours for a particular dose. Assessments according to the order of responses were as follows:

Table 9: Pain-measuring model - Trial 2

Responses	Scalar Value
NNN	0
NNP	1
NNC	2
NPP	3
NPC	4
PPP	5
NCC	6
PPC	7
PCC	8
CCC	9

Of 102 patients entered in the Trial, 3 were lost to follow up and complete demographic data for another two was not available thus 96 patients with pain and 97 with anxiety data were considered in the demographic analysis.

The Kruskal-Wallis test applied to the data for pain and anxiety relief revealed that the meprobamate, ethoheptazine-aspirin combination was significantly more effective ($P<0.001$) than the other two treatments combined in relieving pain and was significantly superior ($P<0.01$) to the ethoheptazine –aspirin combination in relieving anxiety.

Chi-square analysis revealed that the that the meprobamate, ethoheptazine-aspirin combination was significantly more effective($P<0.001$) than the other two treatments combined in relieving pain and was significantly superior ($P<0.01$) to the ethoheptazine –aspirin combination in relieving anxiety.

In applying Cochran's Test for Related Observations, scalar values of 7 or greater were considered a success; all others a failure. The test revealed that the ethoheptazine –aspirin meprobamate was significantly superior $P<0.005$) to the other two agents in relieving pain.

Trial 3: (1975)

Winkelman JR, Richards DJ. Double blind evaluation of an analgesic-tranquilliser combination for treating musculoskeletal pain associated with anxiety. Curr Ther Res 1975; 17(4): 352-9

Type of Study.

A Double-Blind, placebo-controlled one-week study, a combination of meprobamate-ethoheptazine –aspirin was compared with, ethoheptazine-aspirin and meprobamate and placebo in the treatment of 90 anxious, psychoneurotic patients with musculoskeletal pain.

Method:

90 men, women with a mean age of 52,5 years seen as out patients. All patients were suffering from anxiety neurosis associated with back, neck or shoulder pain. Patients were assigned to one of four groups accordingly to a previously randomized design.

Group1: Treated with meprobamate 150mg-ethoheptazine 75mg-aspirin 250mg.(N=21)

Group2; Treated with ethoheptazine75mg-aspirin 250mg (N=23)

Group 3: Treated with meprobamate 150mg (N=24)

Group 4: Treated with placebo. (N=22)

Dose:

All medication administered was of uniform size and appearance. Patients were instructed to take 2 tablets four times a day of their assigned medication during the 7 day study. Intensity of pain was rated at baseline and after 2 and 7 days. The intensity of pain and anxiety of each patient at baseline was rated as severe, moderate, mild or absent. Relief was rated as complete, marked, slight or none.

Results:

When effect on pain was compared among the 4 groups at day 2 and day 7, group 2 showed the highest percentage in reduction of pain intensity.

Table 10: Percentage reduction in the intensity of pain - Trial 3

Day of assessment	Group			
	1	2	3	4
2	67%	78%	29%	14%
7	62%	74%	29%	14%

These results were analyzed using the log likelihood ratio test:

In this study there was no apparent relationship between the tranquilizer and analgesic effect and no apparent interaction of the analgesic and tranquilizer in producing pain relief on either day.

Table 11: Percentage reduction in the severity of anxiety - Trial 3

Day of assessment	Group			
	1	2	3	4
2	81%	39%	46%	32%
7	76%	39%	46%	32%

Application of the log likelihood ratio test showed that remission of anxiety was significantly related to the tranquilizer and the analgesic. Using the Mantel-Haenszel Test, results with the tranquilizer-analgesic were compared to the other three therapies; the combination was found to be significantly more effective than were the others (P,0.003).In addition the combination of meprobamate 150mg-ethoheptazine 75mg-aspirin 250mg was statistically more effective than each component alone, including meprobamate.

Trial 4: (1981)

Fehler BM. Analgesic and antipyretic effects of Stopayne tablets in patients with influenza. . Curr Ther Res 1981; 30(Aug): 147-50.

Type of Study:

A single blind study to assess the analgesic and antipyretic effects of Stopayne (Paracetamol 320mg,Codeine phosphate 8mg,Caffeine alkaloid 48mg, meprobamate 150mg) was under taken in 37 patients suffering from influenza.

Method:

37 men and women with the mean age of 35,1 years suffering from characteristic symptoms of influenza, such as hay fever, headache, myalgia, joint pain etc.

The study lasted 24 hours. The patients were each given a diary in which to record the degree and period of analgesia, as well as the sedative effect.

Dose:

Two tablets every four hours.

Results:

Table 1 shows the frequency of symptoms at the beginning of the study.

Table 12: Percentage of Symptoms

Symptom	Percentage
Muscle Pain	100%
Headache	97%
Pharyngitis	91%
Joint pains (one or more joints)	62%
Retro-orbital pain	62%
Bronchitis	38%
Neck stiffness	35%
Post nasal drip	32%
Chest pain	13,5%

On analysis of the patients diary, Table 2 has the following results.

Table 13: Average time/analgesia - *Trial 4*

Symptom	Time to achieve analgesia	Duration of action
Muscle pain	40 minutes	3,7 hours
Headache	35 minutes	4.1 hours

90% of patients had satisfactory relief of muscle pain, 8% had slight relief and in 2% no relief of pain was obtained.

88% of patients had satisfactory relief of headache, 6% had slight relief and in 6% of patients no effect was noted.

Trial 5: (1982)

Stein A Stopayne in the treatment of postoperative pain following gynaecological and obstetric procedures. Curr Ther Res 1982; 32(2): 300-4.

Type of Study:

Single- blind Trial to assess the analgesic and muscle –relaxant effects of stopayne tablets following gynaecological or obstetric surgery

Method:

40 female patients of mean age of 30.8 randomly selected for the study which was conducted over 10 months. Patients were seen in the consulting room or were referred directly to the hospital after consultation with the patients doctor. Patients were questioned on the analgesic response using a four -point scale from complete analgesia to no effect. They also filled out 3 linear assessment forms on three different occasions following surgery.

The first forms were filled out immediately following surgery, and before the first dose of stopayne tablets. The second and third forms had been completed after medication had been taken for day 1 and day 2 respectively.

The patient indicated by means of a cross on a linear scale from 0 to 10, the degree of pain she was experiencing. Patients also noted the time for analgesia to occur as well as the duration of analgesia. Patients also noted if sedating and muscle – relaxant effects were present and if they were able to fall asleep following the night dose.

Dose:

In those cases where major pelvic surgery was carried out, pethidine was used for the first 24 hours post – operatively and then 2 stopayne tablets four-hourly were prescribed for the following 2 days.

In cases of minor surgery, such as dilatation and curettage and episiotomy were performed, stopayne was prescribed on the day of the operation and for 2 days thereafter in the dosage of two tablets 4 hourly.

Results:

Table 14: Analysis of operation types performed - Trial 5

Type of Operation	No. of cases
Major surgery:	
Caesarean section	12
Abdominal hysterectomy	3
Vaginal hysterectomy	2
Ovarian cystectomy	2
Anterior and post Colporraphy	1
Other procedures	3
Total	**23**
Minor Surgery;	
Dilatation and curettage	6
Episiotomy	9
Marsupialization – Bartholin cyst	1
Cone biopsy	1
Total	**17**

On analysis of the data where patients had been asked about the degree of pain relief it was found that after stopayne statistically significant analgesia was obtained ($p<0.01$) in 27,5% of cases, a satisfactory response in 61,25% of cases and a slight effect in 11,25% of patients.

Using the linear method of pain expression there was significant relief for both days with a 33% and 67% reduction for the first and second days respectively. For the two days of the study average time for analgesia to occur was 22 minutes and the average period of analgesia was 4.3 hours. 37 of the 40 patients were aware of muscle-relaxant effect.

Table 15: Degree of analgesia - Trial 5

	Complete	Satisfactory	Slight
Day 1	15.0%	65.0%	20.0%
Day 2	40.0%	57,5%	2.5%
Average for 2 days	27.5%	61.25%	11.25%

Table 16: Efficacy of Stopayne - Trial 5

Effects	Day 1	Day 2	Average % Response
Muscle relaxation	87.5%	97.5%	92.5%
Sedation	87.0%	100.0%	93.5%
Sleep	80.0%	92.5%	86.2%

Trial 6: (1982)

Hossy SC, de Kock M. Treatment of postoperative pain with a combination analgesic: Stopayne tablets. Curr Ther Res 1982; 32(5): 633-7.

Type of study:

A single blind surgical study conducted in two centres, Johannesburg and Cape Town to assess the analgesic effect of Stopayne Tablets.

Method:

51 patients selected over 6 months. Mean age of patients was 36.7 years. Only surgical patients were selected and procedures were varied from elective surgery such as appendicectomy and varicose vein stripping, to emergency procedures such as amputations and skin grafting in patients with extensive burns.

Patients were assess for 2 days immediately following surgery at a dose of 2 tablets four hourly as required.

Investigators recorded the assessment of time for analgesia to occur, period of analgesia, muscle relaxation, effects on sleep and degree of analgesia to occur.

The degree of pain felt was indicated using a visual analogue scale while the assessment of the degree of analgesia was expressed on a 4-point scale.

Dose:

Two tablets four-hourly.

Results:

Table 17: Types of operation included in the trial.

Type of operation	Number of cases.
Orthopaedic procedures	9
Plastic surgery	6
Varicose vein stripping	5
Partial mastectomy	3
Inguinal hernia	3
Rectal surgery	3
Appendicectomy	3
Cervical sympathectomy	1
Parotidectomy	1
Other	17

Pethidine was prescribed for the first 24 hours after which stopayne was the only analgesic used. Complete pain relief was obtained in 25.5% of cases by day 1, and in 40% by day 2.

On analysis of the linear assessment of pain there was a 57% and 73% reduction in pain experienced over the first and second day, respectively.

Table 18: Degree of analgesia obtained by stopayne tablets - Trial 6

	Complete	Satisfactory	Slight	None
Day 1	25,5%	56,8%	15,7%	2,0%
Day 2	40,0%	56,0%	4,0%	Nil
Average for 2 days.	32,7%	56,4%	9,9%	1,0%

Table 19: Time until analgesia occurred - Trial 6

	Day 1	Day 2	Day 3
Time for analgesia to occur	20,10 mins.	18,9 mins.	20,0 mins.
Period of analgesia	3,6 hours	4,0 hours	3,8 hours

Table 20: Efficacy of stopayne tablets - Trial 6

	Day 1	Day 2	Average
Muscle relaxation	54.9%	54.0%	54.5%
Sedation	62.7%	60.0%	61.4%
Sleep	76.5%	88.0%	82.2%
Sleep resumes	73.9%	86.7%	80.2%

Trial 7:(1984)

Nel G. Treatment of postoperative pain in orthopaedic patients with Stopayne Tablets. Curr Ther Res 1984; 36(4): 773-8.

Type of Study:

Open study of 18 patients to assess the analgesic effects of stopayne in patients who under went orthopaedic surgery.

Method:

18 patients were evaluated over a period of 2 to 5 days after orthopaedic surgery. Patients who had undergone surgery under a general anaesthetic were included in the trial. Pethidine or morphine was administered for the initial 24-hour post operative period for those who underwent a general anaesthetic. The patients were asked to rate their pain relief on a verbal scale as well as a visual analogue scale by means of a mark on an un-calibrated 10cm line.

The first assessment was made after the operation but before any stopayne tablets had been taken and served as a baseline assessment.

For the verbal scale:-Point 0,1,2,3 meant no relief, slight relief, satisfactory relief and complete relief respectively.(PR)

For the visual analogue scale:-Subtraction of the assessment value from the baseline value, termed the Pain Analogue Difference (PAD) was measured in centimetres. Theoretically the PAD is a number that could range from -10cm to +10cm.

Patients also recorded the time taken for the analgesic effect to be noticed, the duration of the analgesic effect and whether any relaxing effect or effect on sleep occurred.

Dose:

After the initial 24-hour post operative period stopayne tablets were administered as required at a maximum dose of two tablets four-hourly.

Results:

Not all patients remained in the trial for 5 days. Pain relief experienced by the patients was assessed both verbally (PR) and by pain analogue difference (PAD) . A comparison between the two methods was facilitated by converting the PAD scale to a scale from 0 to 3 by multiplying all PAD scores by a factor of 0,3.The converted scale is indicated by PADC.

For each day the average verbal PR score per patient as well as the average PADC score per patient was determined. These values are reflected in Table 17.

Table 21: Pain relief assessment over time - Trial 7

	Day 1	Day 2	Day 3	Day 4	Day 5
Number of patients in study	16	18	15	10	4
Mean PR per patient	1,68	2,06	2,13	2,20	2,25
Mean PAD	2,07	4,03	5,06	5,2	6,4
Mean PADC per patient.	0,62	1,21	1,52	1,56	1,92

The average duration of the analgesic effect over the entire study was 3,9 hours. A sedative effect was reported in 42 (60,9%) out of a total of 69 assessments made over the five days of study.

Effect on sleep:- In 49 (76,6%) out of a total of 64 assessments, which were made over the five days of the study, patients, declared that the tablets helped them to sleep. On 58 occasions patients awoke with pain during the night. In 44 of these instances the patients were able to fall asleep again after taking the tablets.

On the first day of the study the most frequently administered dose was eight tablets while on each of the following days, most patients took six tablets.

Trial 8:(1984)

Earle JW. A study on the analgesic effects of Stopayne in patients who have undergone neurosurgery. Curr Ther Res 1984;36(3);449-455.

Type of study:

An open study on 29 patients who had undergone either spinal or cranial surgery.

Method:

Patients who had undergone neurosurgery under general or spinal anaesthesia were included in the trial design. On the first postoperative day patients were given opiate analgesics such as pethidine. Stopayne tablets were given as required to a maximum dose of two tablets four hourly.

Records were completed at the end of each day by doctor and patient on aspects of pain relief and number of tablets taken. Patients took part in the trial for a minimum of 2 and a maximum of 5 days.

Dose:

As required to a maximum of two tablets four-hourly.

Results:

As in Trial 7, patients were asked to rate their pain relief (PR) on the following verbal scale to which the indicated numerical scores were assigned: complete relief =3,satisfactory relief =2, slight relief =1, and no relief =0

The patients were also asked to indicate pain intensity on a linear pain analogue scale by means of a mark on an uncalibrated 10cm line of which the left -hand end point represented no pain at all and the right hand end point pain could not be more severe. The first assessment was made after the operation but before any Stopayne tablets were taken and served as a baseline value.

Subsequent assessments were made at the end of each day of participation in the study and subtraction of these assessments from the baseline values, termed the pain analogue difference (PAD) and measured in centimetres provided measure of pain relief experienced on the respective days.

Patients were also asked at the end of each day about the time it took for the analgesic effect to occur, the duration of analgesic effect, and whether any relaxing effect or effect on sleep was noticed a record was kept of the number of tablets used. A comparison between the two methods was facilitated by converting the PAD scale to a scale from 0 to 3 by multiplying all PAD scores by a factor of 0,3.The converted scale is indicated by PADC.

For each day the average verbal PR score per patient as well as the average PADC score per patient was determined. These values are reflected in Table 18.

Table 22: Pain relief assessment over time - Trial 8

	Day 1	Day 2	Day 3	Day 4	Day 5
Number of patients in study	22	22	19	10	7
Mean PR per patient	1,77	2,00	2,21	2,3	2,14
Mean PAD	2,93	3,73	4,3	4,76	5,33
Mean PADC per patient.	0,88	1,12	1,29	1,43	1,60

The average duration of the analgesic effect over the entire study was 4,6 hours. A sedative effect was reported in 100 (87,7%) out of a total of 114 assessments made over the five days of study.

Effect on sleep:- In 81 (75,7%) out of a total of 107 assessments which were made over the five days of the study, patients declared that the tablets helped them to sleep.

The most frequently administered dose was the same for each of the following days, most patients took six tablets per day.

Trial 9: (1985)

Bloch B, Smythe E, Weeks R. SAMJ 1985;67:325-9.

Type of study:

A two phase double – blind study was performed to assess the efficacy of 2 oral preparations, compound A, Stopayne Tablets (paracetamol 320mg,caffeine 32mg,codeine phosphate 8mg and meprobamate 150mg) and compound B Baralgan HS (Dipyrone 500mg,pitofenone hydrochloride 5mg and fenpiverinium bromide 0,1mg) . Also in the second phase the parenteral administration of pethidine 100mg and dipyrone 2 500mg. The assessment was done on patients who had undergone abdominal hysterectomy.

Method: Phase 1:

169 patients were analysed.84 receiving compound A and 85 receiving compound B. Both compound were made up as identical tablets and allocated according to a randomised code. The study was conducted in a double blind parallel way. Treatment allocation was constructed in blocks of 4 and stratified for smokers and non-smokers.

Each patient initially received 2 tablets, this dose being administered when the patient requested analgesia and was able to take oral medication. Subsequent tablets were taken as and when required for pain relief. The trial lasted for a maximum of 54 hours postoperatively and alternate analgesia was provided if requested by the patient.

Phase II:

Not relevant to the topic.

Pain scale:- each patient recorded the degree of pain on a visual analogue scale with a 10cm line with "no pain" at the left extremity and "worst pain" at the right extremity.

Sedation scale- a visual analogue sedation scale, also a 10cm line, with "fully awake" at the left extremity and "asleep" at the right extremity.

Pain score-observer estimated pain severity with the following gradings: 1 – no discomfort, patient at complete ease; 2 – quiet, eyes closed and avoiding movement; 3- strained facial expression, avoiding movement; and 4-writhing, sweating, distressed.

Pain relief –observer estimated efficacy of pain relief.

Side effects were recorded on the patient record form.

The assessments listed were recorded immediately before administration of the analgesic and thereafter at 30 and 60 minutes and 2,3,4,5 and 6 hours after administration.

Each patient was supplied with sufficient tablets of the trial analgesic, for the next 48 hours and self administration of the tablets was encouraged with a minimum of 4 hours between doses.

Results:

The variables defined to measure the overall effect were:

The Total Pain Score - TPS - the sum of the pain scores at 30,60,120,180, and 240 minutes.

Total pain relief – TPR - the sum of pain relief scores at 30,60,120,180, and 240 minutes.

TPPS – the sum of pain levels as recorded on the visual analogue sedation scale at 30,60,120,180, and 240 minutes.

TPSS – the sum of sedation levels as recorded on the visual analogue sedation scale at 30,60,120,180, and 240 minutes.

Table 23: Pain relief assessment - Trial 9

Variable	Compound A N=84	Compound B N=85	Statistical test	*P* value
TPS	-5,68	-5,91	TWAOV	0,5177
TPR	16,12	16,85	TWAOV	0,2763
TPPS	-173,93	-167,91	TWAOV	0,6140
TPSS	266,22	243,48	TWAOV	0,2211
Side effects present	21,4%	12,9%	X^2	0,1583
No concomitant medication taken	81,0%	65,9%	X^2	0,0411
Second dose before 6 hours	26,2%	41,2%	X^2	0,0577
Total No number of tablets taken	13,17	14,60	TWAOV	0,0054

In this study there was no statistically significant difference between patients receiving compound A and B as regards the observations when compared by a two – way analysis of variance, the respective p values being 0,52; 0,28; 0,61; and 0,22.

When smokers and non- smokers were compared all parameters also showed no statistically significant difference between these groups.

A statistically significant smaller percentage of patients taking compound A needed a second dose before the initial 6- hour period had passed.(26,2% vs 41,2%;*p*=0,0577)

A greater percentage receiving compound B took concomitant medication (34,1% vs 19,0% ;p=0,0411).Both these factors were probably operative and significant in the other observation that is statistically significant, i.e. that on average fewer tablets of compound A than of compound B were taken. Overall, however, if all analyses are considered jointly, there is very little difference between these two drug combinations as regards relief of post operative pain.

Trial 10 (1987)

Braun SA Stopayne for postoperative pain in plastic surgery patients. SAMJ 1987;72 (6);394-395.

Type of Study:

A 2 –day open study to assess the safety and efficacy of Stopayne Tablets conducted in 23 postoperative plastic surgery patients.

Method:

Study population comprised 23 patients of a mean age of 31,9 years who had undergone plastic surgery and whose pain was considered moderate to severe.

Some of the patients received pethidine or papaveretum postoperatively. There after at the patients' request, but not less than 3 hours after the injection 2 stopayne tablets were given. The treatment regimen was repeated 4 hourly as required.

Immediately before the stopayne tablets were administered the baseline subjective pain score was recorded.

There were 2 scales used.

A numerical scale (PR) where the degree of pain relief experienced was assigned to a numerical score as follows – none (o); slight/a little (1); satisfactory/ a lot (2);complete (3):

A linear pain analogue difference scale (PAD) consisting of an uncalibrated 10cm line marked " no pain at all" at the left hand end- point and "pain could not be more severe" at the right hand end point .The difference between the baseline value and the subsequent assessment provided a measure of the pain relief experienced.

The pain experienced was recorded 1 hour after taking the tablets and at the end of the first post-operative day. A baseline pain score for the second post operative day was recorded on awakening and the pain experienced was recorded at the end of the day.

Recorded was the degree of pain relief, time taken for analgesia to occur, period of analgesia, and the number of tablets taken.

Results:

Results of the two methods, PR and PAD, were correlated by converting the PAD scale to a scale of 0-3 by multiplying all PAD values by a factor of 0,3 (PADC). The average verbal PR score as well the average PADC score per patient was determined for each day of the study.

Table 24: Pain relief assessment over time - Trial 10

	1 hour after taking tablet	End of day 1	End of day 2
Mean PR	1,39	1,69	1,70
Mean PADC	0,62	0,65	0,67
Mean PAD	2,06	2,16	2,23

Using the PR scale, 2 patients (9%) experienced complete pain relief and 19 (82%) satisfactory pain relief after 1 hour of having taken the tablets. One patient (4%) recorded the relief experienced as slight while 1 reported no relief. Over the 2- day study period 46 assessments of pain relief using the PR scale were made.

Using the PAD scale, 87% of patients experienced an average pain reduction of 39% 1 hour after taking the tablets compared with baseline values.

By the end of the first day of the study, 91% of patients reported a decrease in the intensity of pain experienced and by the end of the second post operative day 96%.

The average time for analgesia to occur was 37,7± 6,6 minutes and the average duration of analgesia was 3,8± 0,5 hours.

Five patients (22%) rated the analgesia produced by Stopayne as 'excellent' while 15 (65%) recorded it as 'good'. Stopayne was judged to have a' fair' analgesic effect by 2 patients(9%) and 1 patient (4%) rated it as 'poor'.

Two patients complained of drowsiness. No other side effects were reported.

Appendix C: Sales Data of Meprobamate-containing analgesics

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
1	1992	Tabs	20	82,000	1,640,000	625,000	1,993,367	1,163,477	0.38
2	1992	Tabs	20	0	0	0	0	0	0.00
2	1992	Tabs	500	0	0	0	0	0	0.00
3	1992	Tabs	10	0	0	0	0	0	0.00
4	1992	Tabs	20	0	0	0	0	0	0.00
4	1992	Tabs	100	0	0	0	0	0	0.00
4	1992	Tabs	500	0	0	0	0	0	0.00
5	1992	Tabs	100	0	0	0	0	0	0.00
5	1992	Tabs	500	0	0	0	0	0	0.00
6	1992	Tabs	20	3,200	64,000	31,700	77,790	59,012	0.50
7	1992	Tabs	20	1,000	20,000	7,300	24,309	13,589	0.37
7	1992	Tabs	100	3,600	360,000	109,900	437,568	204,586	0.31
7	1992	Tabs	1000	50	50,000	20,500	60,773	38,162	0.41
8	1992	Tabs	100	0	0	0	0	0	0.00
8	1992	Tabs	500	300	150,000	20,200	182,320	37,604	0.13
9	1992	Tabs	20	2,100	42,000	32,300	51,050	60,129	0.77
10	1992	Tabs	30	2,500	75,000	14,600	91,160	27,179	0.19
10	1992	Tabs	100	4,200	420,000	66,000	510,496	122,863	0.16
10	1992	Tabs	500	600	300,000	38,800	364,640	72,229	0.13
11	1992	Tabs	100	0	0	0	0	0	0.00
12	1992	Caps	20	2,400	48,000	14,000	58,342	26,062	0.29
12	1992	Caps	100	2,200	220,000	62,200	267,403	115,789	0.28
13	1992	Tabs	20	0	0	0	0	0	0.00
13	1992	Tabs	100	0	0	0	0	0	0.00
14	1992	Tabs	1000	0	0	0	0	0	0.00
15	1992	Caps	100	4,900	490,000	142,700	595,579	265,645	0.29
16	1992	Tabs	20	20,900	418,000	140,600	508,065	261,736	0.34
16	1992	Tabs	200	1,600	320,000	90,600	388,950	168,658	0.28
16	1992	Tabs	500	2,800	1,400,000	365,900	1,701,654	681,146	0.26
17	1992	Tabs	100	30,400	3,040,000	527,500	3,695,021	981,975	0.17
17	1992	Tabs	1000	17,000	17,000,000	2,292,900	20,662,946	4,268,379	0.13
18	1992	Caps	100	7,400	740,000	195,900	899,446	364,680	0.26
18	1992	Caps	500	2,400	1,200,000	245,900	1,458,561	457,758	0.20
19	1992	Tab	100	293,500	29,350,000	13,112,700	35,673,969	24,410,125	0.45
20	1992	Caps	100	153,300	15,330,000	6,849,800	18,633,116	12,751,338	0.45
21	1992	Tabs	10	0	0	0	0	0	0.00
21	1992	Caps	20	33,400	668,000	264,800	811,932	492,942	0.40
22	1992	Caps	20	12,500	250,000	117,800	303,867	219,292	0.47
22	1992	Caps	100	5,700	570,000	256,300	692,816	477,119	0.45
22	1992	Caps	500	34	17,000	6,900	20,663	12,845	0.41
23	1992	Tabs	20	3,200	64,000	18,400	77,790	34,253	0.29
23	1992	Tabs	100	17,500	1,750,000	479,500	2,127,068	892,620	0.27
24	1992	Tabs	20	8,300	166,000	48,500	201,768	90,286	0.29
24	1992	Tabs	100	61,400	6,140,000	1,675,000	7,462,970	3,118,119	0.27
24	1992	Tabs	500	10,900	5,450,000	1,440,100	6,624,298	2,680,838	0.26
25	1992	Caps	20	4,400	88,000	21,900	106,961	40,768	0.25
25	1992	Caps	100	13,200	1,320,000	317,000	1,604,417	590,116	0.24
25	1992	Caps	500	700	350,000	78,000	425,414	145,202	0.22
26	1992	Caps	500	0	0	0	0	0	0.00
27	1992	Tabs	20	0	0	0	0	0	0.00
27	1992	Tabs	500	0	0	0	0	0	0.00

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
28	1992	Tabs	25	9,200	230,000	154,800	279,558	288,170	0.67
1	1993	Tabs	20	54,200	1,084,000	286,400	1,289,318	486,632	0.26
1	1993	Tabs	100	6,900	690,000	112,700	820,692	191,492	0.16
2	1993	Tabs	20	0	0	0	0	0	0.00
2	1993	Tabs	500	0	0	0	0	0	0.00
4	1993	Tabs	20	3,000	60,000	28,000	71,364	47,576	0.47
4	1993	Tabs	100	2,000	200,000	81,000	237,882	137,630	0.41
4	1993	Tabs	500	0	0	0	0	0	0.00
5	1993	Tabs	100	100	10,000	6,300	11,894	10,705	0.63
5	1993	Tabs	500	800	400,000	98,100	475,763	166,685	0.25
6	1993	Tabs	20	600	12,000	6,200	14,273	10,535	0.52
6	1993	Tabs	500	26	13,000	5,300	15,462	9,005	0.41
7	1993	Tabs	20	1,500	30,000	11,200	35,682	19,030	0.37
7	1993	Tabs	100	3,400	340,000	111,100	404,399	188,774	0.33
7	1993	Tabs	1000	100	100,000	29,000	118,941	49,275	0.29
8	1993	Tabs	100	0	0	0	0	0	0.00
8	1993	Tabs	500	200	100,000	18,200	118,941	30,924	0.18
9	1993	Tabs	20	100	2,000	1,800	2,379	3,058	0.90
10	1993	Tabs	30	3,200	96,000	21,300	114,183	36,192	0.22
10	1993	Tabs	100	540	54,000	9,000	64,228	15,292	0.17
10	1993	Tabs	500	1,100	550,000	66,300	654,174	112,653	0.12
11	1993	Tabs	100	0	0	0	0	0	0.00
12	1993	Caps	20	2,100	42,000	13,300	49,955	22,598	0.32
12	1993	Caps	100	2,500	250,000	71,400	297,352	121,318	0.29
13	1993	Tabs	20	1,500	30,000	12,500	35,682	21,239	0.42
13	1993	Tabs	100	5,500	550,000	196,200	654,174	333,370	0.36
14	1993	Tabs	1000	0	0	0	0	0	0.00
15	1993	Caps	100	6,700	670,000	209,400	796,903	355,798	0.31
16	1993	Tabs	20	13,100	262,000	97,300	311,625	165,326	0.37
16	1993	Tabs	200	600	120,000	35,100	142,729	59,640	0.29
16	1993	Tabs	500	2,100	1,050,000	285,900	1,248,878	485,782	0.27
17	1993	Tabs	100	39,700	3,970,000	749,800	4,721,950	1,274,010	0.19
17	1993	Tabs	1000	16,700	16,700,000	2,527,200	19,863,115	4,294,049	0.15
18	1993	Caps	100	9,800	980,000	289,800	1,165,620	492,409	0.30
18	1993	Caps	500	2,300	1,150,000	260,900	1,367,819	443,304	0.23
19	1993	Tab	100	233,700	23,370,000	11,290,500	27,796,467	19,184,061	0.48
20	1993	Caps	100	125,000	12,500,000	6,044,700	14,867,601	10,270,749	0.48
21	1993	Caps	20	26,600	532,000	251,500	632,765	427,332	0.47
22	1993	Caps	20	8,000	160,000	84,700	190,305	143,917	0.53
22	1993	Caps	100	8,500	850,000	422,900	1,010,997	718,563	0.50
22	1993	Caps	500	10	5,000	3,800	5,947	6,457	0.76
23	1993	Tabs	20	3,300	66,000	27,300	78,501	46,386	0.41
23	1993	Tabs	100	15,400	1,540,000	563,400	1,831,688	957,292	0.37
24	1993	Tabs	20	5,000	100,000	41,900	118,941	71,194	0.42
24	1993	Tabs	100	54,700	5,470,000	2,008,100	6,506,062	3,412,029	0.37
24	1993	Tabs	500	10,200	5,100,000	1,712,400	6,065,981	2,909,595	0.34
25	1993	Caps	20	3,100	62,000	25,800	73,743	43,838	0.42
25	1993	Caps	100	12,700	1,270,000	464,400	1,510,548	789,077	0.37
25	1993	Caps	500	800	400,000	134,000	475,763	227,684	0.34
26	1993	Caps	500	16	8,000	4,000	9,515	6,797	0.50
27	1993	Tabs	20	0	0	0	0	0	0.00
27	1993	Tabs	500	0	0	0	0	0	0.00
28	1993	Tabs	25	7,200	180,000	150,400	214,093	255,550	0.84
1	1994	Tabs	20	19,800	396,000	184,600	460,906	285,471	0.47

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Value	Rand Value per Tab/Cap
1	1994	Tabs	100	20,300	2,030,000	356,800	2,362,723	551,766	0.18
2	1994	Tabs	20	0	0	0	0	0	0.00
2	1994	Tabs	500	0	0	0	0	0	0.00
4	1994	Tabs	20	1,200	24,000	9,400	27,934	14,536	0.39
4	1994	Tabs	100	1,100	110,000	44,300	128,029	68,507	0.40
4	1994	Tabs	500	0	0	0	0	0	0.00
5	1994	Tabs	20	2,800	56,000	17,000	65,179	26,289	0.30
5	1994	Tabs	500	1,700	850,000	199,900	989,318	309,131	0.24
6	1994	Tabs	20	1,900	38,000	17,900	44,228	27,681	0.47
7	1994	Tabs	20	1,200	24,000	9,300	27,934	14,382	0.39
7	1994	Tabs	100	3,500	350,000	119,200	407,366	184,334	0.34
7	1994	Tabs	1000	600	600,000	128,900	698,342	199,335	0.21
8	1994	Tabs	100	0	0	0	0	0	0.00
8	1994	Tabs	500	400	200,000	36,900	232,781	57,063	0.18
9	1994	Tabs	20	300	6,000	4,500	6,983	6,959	0.75
9	1994	Tabs	100	300	30,000	12,800	34,917	19,794	0.43
10	1994	Tabs	30	2,700	81,000	19,900	94,276	30,774	0.25
10	1994	Tabs	100	5,700	570,000	98,900	663,425	152,942	0.17
10	1994	Tabs	500	1,300	650,000	81,000	756,537	125,261	0.12
11	1994	Tabs	100	0	0	0	0	0	0.00
12	1994	Caps	20	1,900	38,000	14,600	44,228	22,578	0.38
12	1994	Caps	100	3,000	300,000	106,800	349,171	165,159	0.36
13	1994	Tabs	20	2,200	44,000	17,300	51,212	26,753	0.39
13	1994	Tabs	100	5,400	540,000	187,300	628,508	289,646	0.35
14	1994	Tabs	20	700	14,000	9,600	16,295	14,846	0.69
15	1994	Caps	100	3,800	380,000	136,000	442,283	210,314	0.36
16	1994	Tabs	20	6,900	138,000	57,700	160,619	89,229	0.42
16	1994	Tabs	200	400	80,000	22,100	93,112	34,176	0.28
16	1994	Tabs	500	2,100	1,050,000	309,500	1,222,098	478,620	0.29
17	1994	Tabs	100	57,900	5,790,000	1,041,700	6,738,998	1,610,915	0.18
17	1994	Tabs	1000	20,700	20,700,000	3,418,500	24,092,792	5,286,467	0.17
18	1994	Caps	100	13,100	1,310,000	397,900	1,524,713	615,324	0.30
18	1994	Caps	500	2,800	1,400,000	324,200	1,629,464	501,352	0.23
19	1994	Tab	100	189,600	18,960,000	9,935,400	22,067,601	15,364,390	0.52
20	1994	Caps	100	115,600	11,560,000	5,775,700	13,454,719	8,931,710	0.50
21	1994	Caps	20	24,600	492,000	256,600	572,640	396,814	0.52
22	1994	Caps	20	7,800	156,000	85,800	181,569	132,684	0.55
22	1994	Caps	100	6,700	670,000	356,000	779,815	550,529	0.53
23	1994	Tabs	20	4,500	90,000	43,100	104,751	66,651	0.48
23	1994	Tabs	100	17,300	1,730,000	751,600	2,013,552	1,162,296	0.43
24	1994	Tabs	20	4,200	84,000	41,600	97,768	64,331	0.50
24	1994	Tabs	100	52,800	5,280,000	2,293,100	6,145,408	3,546,116	0.43
24	1994	Tabs	500	11,000	5,500,000	2,092,300	6,401,467	3,235,593	0.38
25	1994	Caps	20	7,000	140,000	68,100	162,946	105,312	0.49
25	1994	Caps	100	15,400	1,540,000	666,900	1,792,411	1,031,313	0.43
25	1994	Caps	500	1,400	700,000	263,700	814,732	407,793	0.38
26	1994	Caps	500	5	2,500	1,600	2,910	2,474	0.64
27	1994	Tabs	20	7,200	144,000	25,300	167,602	39,125	0.18
27	1994	Tabs	500	300	150,000	25,800	174,585	39,898	0.17
28	1994	Tabs	25	4,600	115,000	107,100	133,849	165,623	0.93
1	1995	Tabs	100	29,700	2,970,000	524,800	3,382,658	759,215	0.18
2	1995	Tabs	20	200	4,000	1,400	4,556	2,025	0.35
2	1995	Tabs	500	19	9,500	2,900	10,820	4,195	0.31
4	1995	Tabs	20	1,400	28,000	11,800	31,890	17,071	0.42

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Value	Rand Value per Tab/Cap
4	1995	Tabs	100	2,200	220,000	83,800	250,567	121,231	0.38
4	1995	Tabs	500	0	0	0	0	0	0.00
5	1995	Tabs	20	800	16,000	4,900	18,223	7,089	0.31
5	1995	Tabs	100	500	50,000	9,300	56,947	13,454	0.19
5	1995	Tabs	500	2,200	1,100,000	195,500	1,252,836	282,825	0.18
6	1995	Tabs	20	500	10,000	5,100	11,389	7,378	0.51
7	1995	Tabs	20	1,300	26,000	10,400	29,612	15,045	0.40
7	1995	Tabs	100	3,200	320,000	108,500	364,461	156,964	0.34
7	1995	Tabs	1000	700	700,000	151,800	797,259	219,605	0.22
8	1995	Tabs	100	0	0	0	0	0	0.00
8	1995	Tabs	500	300	150,000	31,900	170,841	46,149	0.21
9	1995	Tabs	20	200	4,000	3,000	4,556	4,340	0.75
9	1995	Tabs	1000	100	100,000	31,400	113,894	45,426	0.31
10	1995	Tabs	30	1,700	51,000	13,600	58,086	19,675	0.27
10	1995	Tabs	100	4,400	440,000	77,700	501,135	112,407	0.18
10	1995	Tabs	500	1,300	650,000	86,600	740,312	125,282	0.13
11	1995	Tabs	100	0	0	0	0	0	0.00
12	1995	Caps	20	1,200	24,000	10,100	27,335	14,611	0.42
12	1995	Caps	100	2,600	260,000	94,600	296,125	136,855	0.36
13	1995	Tabs	20	4,300	86,000	36,800	97,949	53,238	0.43
13	1995	Tabs	100	10,100	1,010,000	365,200	1,150,331	528,325	0.36
14	1995	Tabs	1000	300	300,000	35,800	341,683	51,791	0.12
15	1995	Caps	100	5,700	570,000	227,800	649,197	329,552	0.40
16	1995	Tabs	20	5,200	104,000	47,500	118,450	68,717	0.46
16	1995	Tabs	200	500	100,000	30,500	113,894	44,124	0.31
16	1995	Tabs	500	1,800	900,000	296,300	1,025,048	428,650	0.33
17	1995	Tabs	100	63,500	6,350,000	1,209,000	7,232,282	1,749,029	0.19
17	1995	Tabs	1000	27,400	27,400,000	4,804,200	31,207,012	6,950,112	0.18
18	1995	Caps	100	14,900	1,490,000	263,600	1,697,024	381,343	0.18
18	1995	Caps	500	3,100	1,550,000	361,300	1,765,360	522,683	0.23
19	1995	Tab	100	172,100	17,210,000	9,688,300	19,601,193	14,015,813	0.56
20	1995	Caps	100	103,100	10,310,000	5,620,800	11,742,493	8,131,466	0.55
21	1995	Caps	20	23,200	464,000	246,700	528,469	356,895	0.53
22	1995	Caps	20	6,300	126,000	73,700	143,507	106,620	0.58
22	1995	Caps	100	8,700	870,000	493,600	990,880	714,078	0.57
22	1995	Caps	500	30	15,000	7,600	17,084	10,995	0.51
23	1995	Tabs	20	4,400	88,000	49,800	100,227	72,044	0.57
23	1995	Tabs	100	16,200	1,620,000	819,500	1,845,086	1,185,549	0.51
24	1995	Tabs	20	6,100	122,000	68,600	138,951	99,242	0.56
24	1995	Tabs	100	47,100	4,710,000	2,376,500	5,364,417	3,438,021	0.50
24	1995	Tabs	500	10,500	5,250,000	2,279,200	5,979,446	3,297,260	0.43
25	1995	Caps	20	6,000	120,000	66,900	136,673	96,782	0.56
25	1995	Caps	100	13,800	1,380,000	696,900	1,571,740	1,008,187	0.51
25	1995	Caps	500	2,400	1,200,000	518,000	1,366,730	749,377	0.43
26	1995	Caps	500	55	27,500	18,200	31,321	26,329	0.66
27	1995	Tabs	20	7,800	156,000	27,600	177,675	39,928	0.18
27	1995	Tabs	500	1,700	850,000	137,500	968,101	198,918	0.16
28	1995	Tabs	25	4,500	112,500	118,800	128,131	171,865	1.06
1	1996	Tabs	100	32,800	3,280,000	593,300	3,655,601	784,674	0.18
2	1996	Tabs	20	2,800	56,000	23,200	62,413	30,683	0.41
2	1996	Tabs	500	900	450,000	93,100	501,531	123,130	0.21
4	1996	Tabs	20	1,500	30,000	12,600	33,435	16,664	0.42
4	1996	Tabs	100	3,100	310,000	121,500	345,499	160,691	0.39
4	1996	Tabs	500	10	5,000	1,500	5,573	1,984	0.30

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units 2001	Rand Value	per Tab/Cap
5	1996	Tabs	100	1,300	130,000	22,300	144,887	29,493	0.17
5	1996	Tabs	500	2,400	1,200,000	210,500	1,337,415	278,399	0.18
6	1996	Tabs	20	300	6,000	3,400	6,687	4,497	0.57
7	1996	Tabs	20	1,200	24,000	9,500	26,748	12,564	0.40
7	1996	Tabs	100	3,200	320,000	107,000	356,644	141,514	0.33
7	1996	Tabs	1000	600	600,000	121,400	668,708	160,559	0.20
8	1996	Tabs	100	0	0	0	0	0	0.00
8	1996	Tabs	500	500	250,000	52,000	278,628	68,773	0.21
9	1996	Tabs	20	300	6,000	4,800	6,687	6,348	0.80
9	1996	Tabs	1000	100	100,000	76,300	111,451	100,911	0.76
10	1996	Tabs	30	900	27,000	7,700	30,092	10,184	0.29
10	1996	Tabs	100	3,000	300,000	54,600	334,354	72,212	0.18
10	1996	Tabs	500	1,000	500,000	67,600	557,256	89,405	0.14
11	1996	Tabs	100	0	0	0	0	0	0.00
12	1996	Caps	20	1,100	22,000	8,800	24,519	11,639	0.40
12	1996	Caps	100	2,800	280,000	103,100	312,064	136,356	0.37
13	1996	Tabs	20	4,200	84,000	35,500	93,619	46,951	0.42
13	1996	Tabs	100	8,000	800,000	277,500	891,610	367,010	0.35
14	1996	Tabs	1000	700	700,000	93,500	780,159	123,659	0.13
15	1996	Caps	100	5,200	520,000	214,400	579,547	283,557	0.41
16	1996	Tabs	20	4,300	86,000	40,900	95,848	54,093	0.48
16	1996	Tabs	200	900	180,000	54,500	200,612	72,079	0.30
16	1996	Tabs	500	1,500	750,000	248,800	835,884	329,053	0.33
17	1996	Tabs	100	77,800	7,780,000	1,409,700	8,670,907	1,864,411	0.18
17	1996	Tabs	1000	35,700	35,700,000	6,250,300	39,788,097	8,266,389	0.18
18	1996	Caps	100	14,500	1,450,000	292,500	1,616,043	386,848	0.20
18	1996	Caps	500	4,800	2,400,000	558,300	2,674,830	738,385	0.23
19	1996	Tab	100	175,900	17,590,000	10,970,200	19,604,275	14,508,734	0.62
20	1996	Caps	100	112,200	11,220,000	7,005,500	12,504,830	9,265,185	0.62
21	1996	Caps	20	21,300	426,000	238,500	474,782	315,430	0.56
22	1996	Caps	20	4,600	92,000	58,500	102,535	77,370	0.64
22	1996	Caps	100	8,900	890,000	553,800	991,916	732,433	0.62
22	1996	Caps	500	4	2,000	1,200	2,229	1,587	0.60
23	1996	Tabs	20	4,300	86,000	55,200	95,848	73,005	0.64
23	1996	Tabs	100	16,700	1,670,000	958,500	1,861,236	1,267,673	0.57
24	1996	Tabs	20	6,900	138,000	87,400	153,803	115,592	0.63
24	1996	Tabs	100	45,600	4,560,000	2,613,600	5,082,177	3,456,640	0.57
24	1996	Tabs	500	12,500	6,250,000	3,122,100	6,965,703	4,129,161	0.50
25	1996	Caps	20	3,900	78,000	50,100	86,932	66,260	0.64
25	1996	Caps	100	13,400	1,340,000	769,900	1,493,447	1,018,238	0.57
25	1996	Caps	500	2,700	1,350,000	677,500	1,504,592	896,034	0.50
26	1996	Caps	500	32	16,000	12,400	17,832	16,400	0.78
27	1996	Tabs	20	14,300	286,000	51,400	318,751	67,980	0.18
27	1996	Tabs	500	2,500	1,250,000	207,000	1,393,141	273,770	0.17
28	1996	Tabs	25	4,100	102,500	120,800	114,238	159,765	1.18
1	1997	Tabs	100	33,000	3,300,000	660,800	3,598,992	823,877	0.20
2	1997	Tabs	20	1,000	20,000	8,400	21,812	10,473	0.42
2	1997	Tabs	500	1,300	650,000	131,600	708,892	164,077	0.20
4	1997	Tabs	20	1,100	22,000	12,100	23,993	15,086	0.55
4	1997	Tabs	100	2,100	210,000	84,400	229,027	105,229	0.40
4	1997	Tabs	500	20	10,000	4,100	10,906	5,112	0.41
5	1997	Tabs	100	800	80,000	16,600	87,248	20,697	0.21
5	1997	Tabs	500	1,800	900,000	199,400	981,543	248,609	0.22
6	1997	Tabs	20	200	4,000	2,300	4,362	2,868	0.58

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Value	Rand Value per Tab/Cap
7	1997	Tabs	20	1,900	38,000	14,000	41,443	17,455	0.37
7	1997	Tabs	100	3,300	330,000	99,000	359,899	123,432	0.30
7	1997	Tabs	1000	800	800,000	115,100	872,483	143,505	0.14
8	1997	Tabs	100	75	7,500	1,500	8,180	1,870	0.20
8	1997	Tabs	500	700	350,000	75,800	381,711	94,506	0.22
9	1997	Tabs	20	300	6,000	6,300	6,544	7,855	1.05
9	1997	Tabs	1000	100	100,000	32,200	109,060	40,147	0.32
10	1997	Tabs	30	2,000	60,000	15,400	65,436	19,201	0.26
10	1997	Tabs	100	1,400	140,000	26,900	152,685	33,539	0.19
10	1997	Tabs	500	1,300	650,000	110,600	708,892	137,895	0.17
11	1997	Tabs	100	100	10,000	12,700	10,906	15,834	1.27
12	1997	Caps	20	700	14,000	6,000	15,268	7,481	0.43
12	1997	Caps	100	2,500	250,000	92,600	272,651	115,452	0.37
13	1997	Tabs	20	7,000	140,000	59,400	152,685	74,059	0.42
13	1997	Tabs	100	12,300	1,230,000	441,400	1,341,443	550,332	0.36
14	1997	Tabs	1000	3,100	3,100,000	401,300	3,380,871	500,336	0.13
15	1997	Caps	100	6,500	650,000	265,200	708,892	330,648	0.41
16	1997	Tabs	20	4,000	80,000	38,600	87,248	48,126	0.48
16	1997	Tabs	200	400	80,000	21,200	87,248	26,432	0.27
16	1997	Tabs	500	1,200	600,000	197,300	654,362	245,991	0.33
17	1997	Tabs	100	75,300	7,530,000	1,534,800	8,212,246	1,913,569	0.20
17	1997	Tabs	1000	47,400	47,400,000	9,037,400	51,694,616	11,267,714	0.19
18	1997	Caps	100	16,100	1,610,000	553,800	1,755,872	690,471	0.34
18	1997	Caps	500	5,500	2,750,000	725,200	2,999,160	904,170	0.26
19	1997	Tab	100	131,900	13,190,000	9,293,000	14,385,063	11,586,392	0.70
20	1997	Caps	100	94,500	9,450,000	6,672,200	10,306,205	8,318,813	0.71
21	1997	Caps	20	19,100	382,000	223,200	416,611	278,283	0.58
22	1997	Caps	20	2,700	54,000	38,500	58,893	48,001	0.71
22	1997	Caps	100	9,300	930,000	621,000	1,014,261	774,255	0.67
22	1997	Caps	500	29	14,500	9,400	15,814	11,720	0.65
23	1997	Tabs	20	3,300	66,000	49,000	71,980	61,093	0.74
23	1997	Tabs	100	11,800	1,180,000	799,600	1,286,912	996,931	0.68
24	1997	Tabs	20	4,200	84,000	62,800	91,611	78,298	0.75
24	1997	Tabs	100	33,800	3,380,000	2,288,700	3,686,241	2,853,522	0.68
24	1997	Tabs	500	7,200	3,600,000	2,092,100	3,926,173	2,608,403	0.58
25	1997	Caps	20	2,700	54,000	40,500	58,893	50,495	0.75
25	1997	Caps	100	10,900	1,090,000	742,100	1,188,758	925,241	0.68
25	1997	Caps	500	2,100	1,050,000	599,200	1,145,134	747,075	0.57
26	1997	Caps	500	20	10,000	8,800	10,906	10,972	0.88
27	1997	Tabs	20	23,600	472,000	104,500	514,765	130,289	0.22
27	1997	Tabs	500	2,200	1,100,000	216,600	1,199,664	270,054	0.20
28	1997	Tabs	25	3,800	95,000	118,900	103,607	148,243	1.25
1	1998	Tabs	100	27,500	2,750,000	598,400	2,934,814	684,389	0.22
2	1998	Tabs	20	0	0	0	0	0	0.00
2	1998	Tabs	500	1,000	500,000	104,300	533,603	119,288	0.21
4	1998	Tabs	20	800	16,000	10,500	17,075	12,009	0.66
4	1998	Tabs	100	1,800	180,000	88,100	192,097	100,760	0.49
4	1998	Tabs	500	18	9,000	5,300	9,605	6,062	0.59
5	1998	Tabs	100	0	0	0	0	0	0.00
5	1998	Tabs	500	10	5,000	1,100	5,336	1,258	0.22
6	1998	Tabs	20	200	4,000	2,800	4,269	3,202	0.70
7	1998	Tabs	20	2,100	42,000	15,200	44,823	17,384	0.36
7	1998	Tabs	100	2,200	220,000	63,400	234,785	72,510	0.29
7	1998	Tabs	1000	600	600,000	77,800	640,323	88,980	0.13

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Value	Rand Value per Tab/Cap
8	1998	Tabs	100	0	0	0	0	0	0.00
8	1998	Tabs	500	800	400,000	88,000	426,882	100,645	0.22
9	1998	Tabs	20	100	2,000	2,600	2,134	2,974	1.30
9	1998	Tabs	1000	50	50,000	15,000	53,360	17,155	0.30
10	1998	Tabs	30	0	0	0	0	0	0.00
10	1998	Tabs	100	2,500	250,000	55,300	266,801	63,247	0.22
10	1998	Tabs	500	1,800	900,000	159,700	960,485	182,649	0.18
11	1998	Tabs	100	700	70,000	50,300	74,704	57,528	0.72
12	1998	Caps	20	400	8,000	3,200	8,538	3,660	0.40
12	1998	Caps	100	1,900	190,000	75,100	202,769	85,892	0.40
13	1998	Tabs	20	400	8,000	3,000	8,538	3,431	0.38
13	1998	Tabs	100	9,800	980,000	353,500	1,045,861	404,297	0.36
14	1998	Tabs	1000	5,600	5,600,000	902,400	5,976,349	1,032,073	0.16
15	1998	Caps	100	6,200	620,000	255,000	661,667	291,643	0.41
16	1998	Tabs	20	3,500	70,000	36,500	74,704	41,745	0.52
16	1998	Tabs	200	200	40,000	10,700	42,688	12,238	0.27
16	1998	Tabs	500	1,300	650,000	209,900	693,683	240,062	0.32
17	1998	Tabs	100	69,900	6,990,000	1,712,200	7,459,765	1,958,240	0.24
17	1998	Tabs	1000	54,200	54,200,000	12,583,000	57,842,524	14,391,158	0.23
18	1998	Caps	100	14,100	1,410,000	611,900	1,504,759	699,829	0.43
18	1998	Caps	500	6,300	3,150,000	1,101,900	3,361,697	1,260,241	0.35
19	1998	Tab	100	114,100	11,410,000	9,163,200	12,176,812	10,479,938	0.80
20	1998	Caps	100	91,000	9,100,000	7,286,900	9,711,568	8,334,016	0.80
21	1998	Caps	20	15,400	308,000	205,700	328,699	235,259	0.67
22	1998	Caps	20	500	10,000	7,000	10,672	8,006	0.70
22	1998	Caps	100	11,100	1,110,000	777,900	1,184,598	889,683	0.70
22	1998	Caps	500	200	100,000	42,200	106,721	48,264	0.42
23	1998	Tabs	20	1,700	34,000	30,100	36,285	34,425	0.89
23	1998	Tabs	100	9,400	940,000	758,600	1,003,173	867,610	0.81
24	1998	Tabs	20	1,900	38,000	34,400	40,554	39,343	0.91
24	1998	Tabs	100	23,500	2,350,000	1,889,100	2,507,932	2,160,561	0.80
24	1998	Tabs	500	3,800	1,900,000	1,323,600	2,027,690	1,513,799	0.70
25	1998	Caps	20	1,700	34,000	30,500	36,285	34,883	0.90
25	1998	Caps	100	8,800	880,000	707,300	939,141	808,938	0.80
25	1998	Caps	500	1,100	550,000	394,600	586,963	451,303	0.72
26	1998	Caps	500	10	5,000	4,100	5,336	4,689	0.82
27	1998	Tabs	20	29,700	594,000	135,800	633,920	155,314	0.23
27	1998	Tabs	500	100	50,000	7,900	53,360	9,035	0.16
28	1998	Tabs	25	700	17,500	24,300	18,676	27,792	1.39
1	1999	Tabs	100	64,100	6,410,000	1,480,000	6,694,042	1,655,564	0.23
2	1999	Tabs	20	0	0	0	0	0	0.00
2	1999	Tabs	500	1,200	600,000	138,100	626,587	154,482	0.23
3	1999	Tabs	20	1,000	20,000	5,200	20,886	5,817	0.26
4	1999	Tabs	20	600	12,000	9,300	12,532	10,403	0.78
4	1999	Tabs	100	1,500	150,000	79,000	156,647	88,371	0.53
4	1999	Tabs	500	10	5,000	4,300	5,222	4,810	0.86
5	1999	Tabs	100	0	0	0	0	0	0.00
5	1999	Tabs	500	1,600	800,000	179,100	835,450	200,346	0.22
6	1999	Tabs	20	0	0	0	0	0	0.00
7	1999	Tabs	20	2,200	44,000	16,600	45,950	18,569	0.38
7	1999	Tabs	100	1,300	130,000	38,400	135,761	42,955	0.30
7	1999	Tabs	1000	500	500,000	77,800	522,156	87,029	0.16
8	1999	Tabs	100	0	0	0	0	0	0.00
8	1999	Tabs	500	600	300,000	81,700	313,294	91,392	0.27

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
9	1999	Tabs	20	10	200	300	209	336	1.50
9	1999	Tabs	1000	50	50,000	24,100	52,216	26,959	0.48
10	1999	Tabs	30	0	0	0	0	0	0.00
10	1999	Tabs	100	0	0	0	0	0	0.00
10	1999	Tabs	500	0	0	0	0	0	0.00
11	1999	Tabs	100	1,000	100,000	46,300	104,431	51,792	0.46
12	1999	Caps	20	400	8,000	6,200	8,354	6,935	0.78
12	1999	Caps	100	1,300	130,000	94,700	135,761	105,934	0.73
13	1999	Tabs	20	0	0	0	0	0	0.00
13	1999	Tabs	100	10,300	1,030,000	371,600	1,075,642	415,681	0.36
14	1999	Tabs	1000	7,100	7,100,000	1,625,000	7,414,617	1,817,764	0.23
15	1999	Caps	100	4,200	420,000	202,900	438,611	226,969	0.48
16	1999	Tabs	20	3,900	78,000	41,800	81,456	46,758	0.54
16	1999	Tabs	200	100	20,000	3,600	20,886	4,027	0.18
16	1999	Tabs	500	2,700	1,350,000	520,300	1,409,822	582,020	0.39
17	1999	Tabs	100	63,100	6,310,000	1,454,000	6,589,611	1,626,480	0.23
17	1999	Tabs	1000	54,000	54,000,000	12,954,500	56,392,864	14,491,218	0.24
18	1999	Caps	100	13,000	1,300,000	637,000	1,357,606	712,564	0.49
18	1999	Caps	500	6,000	3,000,000	1,103,900	3,132,937	1,234,849	0.37
19	1999	Tab	100	99,700	9,970,000	9,196,600	10,411,794	10,287,540	0.92
20	1999	Caps	100	77,200	7,720,000	7,101,500	8,062,091	7,943,910	0.92
21	1999	Caps	20	13,100	262,000	204,300	273,610	228,535	0.78
22	1999	Caps	20	0	0	0	0	0	0.00
22	1999	Caps	100	9,500	950,000	774,200	992,097	866,039	0.81
22	1999	Caps	500	2,000	1,000,000	63,400	1,044,312	70,921	0.06
23	1999	Tabs	20	1,600	32,000	32,300	33,418	36,132	1.01
23	1999	Tabs	100	7,600	760,000	697,700	793,677	780,464	0.92
24	1999	Tabs	20	1,500	30,000	31,300	31,329	35,013	1.04
24	1999	Tabs	100	19,700	1,970,000	1,805,300	2,057,295	2,019,452	0.92
24	1999	Tabs	500	2,900	1,450,000	1,141,000	1,514,253	1,276,350	0.79
25	1999	Caps	20	1,600	32,000	31,600	33,418	35,349	0.99
25	1999	Caps	100	6,600	660,000	601,200	689,246	672,517	0.91
25	1999	Caps	500	1,200	600,000	478,500	626,587	535,262	0.80
26	1999	Caps	500	16	8,000	9,100	8,354	10,179	1.14
27	1999	Tabs	20	30,500	610,000	151,000	637,030	168,912	0.25
27	1999	Tabs	500	0	0	0	0	0	0.00
28	1999	Tabs	25	0	0	0	0	0	0.00
1	2000	Tabs	20	7,000	140,000	66,000	143,068	68,980	0.47
1	2000	Tabs	100	19,300	1,930,000	447,000	1,972,298	467,182	0.23
2	2000	Tabs	500	900	450,000	102,000	459,862	106,605	0.23
3	2000	Tabs	20	600	12,000	3,000	12,263	3,135	0.25
4	2000	Tabs	20	100	2,000	1,000	2,044	1,045	0.50
4	2000	Tabs	100	1,200	120,000	66,000	122,630	68,980	0.55
4	2000	Tabs	500	100	50,000	16,000	51,096	16,722	0.32
5	2000	Tabs	500	1,500	750,000	152,000	766,437	158,863	0.20
6	2000	Tabs	20	100	2,000	2,000	2,044	2,090	1.00
6	2000	Tabs	500	100	50,000	36,000	51,096	37,625	0.72
7	2000	Tabs	20	1,900	38,000	14,000	38,833	14,632	0.37
7	2000	Tabs	100	1,000	100,000	29,000	102,192	30,309	0.29
7	2000	Tabs	1000	900	900,000	190,000	919,724	198,579	0.21
8	2000	Tabs	500	500	250,000	81,000	255,479	84,657	0.32
9	2000	Tabs	20	30	600	1,000	613	1,045	1.67
9	2000	Tabs	1000	70	70,000	30,000	71,534	31,355	0.43
10	2000	Tabs	30	0	0	0	0	0	0.00

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
11	2000	Tabs	100	500	50,000	25,000	51,096	26,129	0.50
12	2000	Caps	20	400	8,000	8,000	8,175	8,361	1.00
12	2000	Caps	100	3,200	320,000	304,000	327,013	317,726	0.95
13	2000	Tabs	100	14,000	1,400,000	503,000	1,430,682	525,710	0.36
14	2000	Tabs	1000	7,800	7,800,000	2,676,000	7,970,945	2,796,822	0.34
15	2000	Caps	20	2,700	54,000	34,000	55,183	35,535	0.63
15	2000	Caps	100	3,100	310,000	168,000	316,794	175,585	0.54
15	2000	Caps	500	1,100	550,000	263,000	562,054	274,874	0.48
16	2000	Tabs	100	100	10,000	2,000	10,219	2,090	0.20
16	2000	Tabs	500	100	50,000	12,000	51,096	12,542	0.24
16	2000	Tabs	1000	6,100	6,100,000	1,248,000	6,233,688	1,304,347	0.20
17	2000	Tabs	100	58,300	5,830,000	1,346,000	5,957,770	1,406,772	0.23
17	2000	Tabs	1000	59,900	59,900,000	13,263,000	61,212,768	13,861,826	0.22
18	2000	Caps	100	13,800	1,380,000	854,000	1,410,244	892,558	0.62
18	2000	Caps	500	5,700	2,850,000	1,110,000	2,912,461	1,160,117	0.39
19	2000	Tabs	100	84,400	8,440,000	8,741,000	8,624,971	9,135,657	1.04
20	2000	Caps	100	61,700	6,170,000	6,376,000	6,305,222	6,663,877	1.03
21	2000	Caps	20	8,800	176,000	166,000	179,857	173,495	0.94
22	2000	Caps	20	600	12,000	9,000	12,263	9,406	0.75
22	2000	Caps	100	4,000	400,000	356,000	408,766	372,073	0.89
22	2000	Caps	500	200	100,000	75,000	102,192	78,386	0.75
23	2000	Tabs	20	1,500	30,000	29,000	30,657	30,309	0.97
23	2000	Tabs	100	12,800	1,280,000	1,108,000	1,308,052	1,158,026	0.87
23	2000	Tabs	500	10	5,000	4,000	5,110	4,181	0.80
24	2000	Tabs	20	1,600	32,000	31,000	32,701	32,400	0.97
24	2000	Tabs	100	35,600	3,560,000	3,190,000	3,638,021	3,334,029	0.90
24	2000	Tabs	500	16,400	8,200,000	6,070,000	8,379,711	6,344,061	0.74
25	2000	Caps	20	1,200	24,000	26,000	24,526	27,174	1.08
25	2000	Caps	100	6,300	630,000	544,000	643,807	568,562	0.86
25	2000	Caps	500	1,400	700,000	449,000	715,341	469,272	0.64
26	2000	Caps	500	15	7,500	9,000	7,664	9,406	1.20
27	2000	Tabs	20	11,500	230,000	73,000	235,041	76,296	0.32
28	2000	Tabs	25	0	0	0	0	0	0.00
1	2001	Tabs	20	1,400	28,000	13,000	28,000	13,000	0.46
1	2001	Tabs	100	21,900	2,190,000	542,000	2,190,000	542,000	0.25
1	2001	Tabs	500	1,800	900,000	215,000	900,000	215,000	0.24
2	2001	Tabs	500	800	400,000	101,000	400,000	101,000	0.25
3	2001	Tabs	20	200	4,000	1,000	4,000	1,000	0.25
3	2001	Tabs	1000	4	4,000	1,000	4,000	1,000	0.25
4	2001	Tabs	20	0	0	0	0	0	0.00
4	2001	Tabs	100	900	90,000	62,000	90,000	62,000	0.69
4	2001	Tabs	500	15	7,500	5,000	7,500	5,000	0.67
5	2001	Tabs	500	1,700	850,000	183,000	850,000	183,000	0.22
6	2001	Tabs	20	300	6,000	5,000	6,000	5,000	0.83
6	2001	Tabs	500	40	20,000	14,000	20,000	14,000	0.70
7	2001	Tabs	20	1,600	32,000	12,000	32,000	12,000	0.38
7	2001	Tabs	100	1,600	160,000	49,000	160,000	49,000	0.31
7	2001	Tabs	1000	1,200	1,200,000	288,000	1,200,000	288,000	0.24
8	2001	Tabs	500	2,400	1,200,000	449,000	1,200,000	449,000	0.37
9	2001	Tabs	20	100	2,000	3,000	2,000	3,000	1.50
9	2001	Tabs	1000	500	500,000	342,000	500,000	342,000	0.68
10	2001	Tabs	100	0	0	0	0	0	0.00
11	2001	Tabs	100	500	50,000	21,000	50,000	21,000	0.42
12	2001	Caps	20	400	8,000	8,000	8,000	8,000	1.00

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
12	2001	Caps	100	700	70,000	63,000	70,000	63,000	0.90
13	2001	Tabs	100	31,700	3,170,000	1,141,000	3,170,000	1,141,000	0.36
14	2001	Tabs	1000	26,300	26,300,000	12,589,000	26,300,000	12,589,000	0.48
15	2001	Caps	20	2,400	48,000	31,000	48,000	31,000	0.65
15	2001	Caps	100	3,900	390,000	232,000	390,000	232,000	0.59
15	2001	Caps	500	1,200	600,000	312,000	600,000	312,000	0.52
16	2001	Tabs	100	300	30,000	8,000	30,000	8,000	0.27
16	2001	Tabs	500	300	150,000	33,000	150,000	33,000	0.22
16	2001	Tabs	1000	14,200	14,200,000	2,916,000	14,200,000	2,916,000	0.21
17	2001	Tabs	100	61,400	6,140,000	1,511,000	6,140,000	1,511,000	0.25
17	2001	Tabs	1000	74,400	74,400,000	16,744,000	74,400,000	16,744,000	0.23
18	2001	Caps	100	12,700	1,270,000	1,030,000	1,270,000	1,030,000	0.81
18	2001	Caps	500	4,400	2,200,000	1,057,000	2,200,000	1,057,000	0.48
19	2001	Tabs	100	89,600	8,960,000	10,393,000	8,960,000	10,393,000	1.16
20	2001	Caps	100	87,700	8,770,000	10,192,000	8,770,000	10,192,000	1.16
21	2001	Caps	20	10,000	200,000	207,000	200,000	207,000	1.04
22	2001	Caps	100	3,800	380,000	395,000	380,000	395,000	1.04
22	2001	Caps	500	500	250,000	192,000	250,000	192,000	0.77
23	2001	Tabs	20	1,800	36,000	46,000	36,000	46,000	1.28
23	2001	Tabs	100	10,000	1,000,000	1,128,000	1,000,000	1,128,000	1.13
23	2001	Tabs	500	0	0	0	0	0	0.00
24	2001	Tabs	20	4,500	90,000	110,000	90,000	110,000	1.22
24	2001	Tabs	100	33,100	3,310,000	3,759,000	3,310,000	3,759,000	1.14
24	2001	Tabs	500	15,600	7,800,000	7,722,000	7,800,000	7,722,000	0.99
25	2001	Caps	20	1,300	26,000	33,000	26,000	33,000	1.27
25	2001	Caps	100	6,200	620,000	711,000	620,000	711,000	1.15
25	2001	Caps	500	1,100	550,000	439,000	550,000	439,000	0.80
26	2001	Caps	500	1,400	700,000	893,000	700,000	893,000	1.28
27	2001	Tabs	20	10,800	216,000	103,000	216,000	103,000	0.48
28	2001	Tabs	25	0	0	0	0	0	0.00
29	2001	Tabs	1000	300	300,000	44,000	300,000	44,000	0.15
31	2001	Caps	30	776,600	23,298,000	38,239,000	23,298,000	38,239,000	1.64
31	2001	Caps	60	240,500	14,430,000	23,672,000	14,430,000	23,672,000	1.64
31	2001	Caps	100	156,100	15,610,000	25,652,000	15,610,000	25,652,000	1.64
32	2001	Tabs	100	157,900	15,790,000	41,469,000	15,790,000	41,469,000	2.63
33	2001	Caps	100	114,600	11,460,000	30,179,000	11,460,000	30,179,000	2.63
34	2001	Tabs	30	169,500	5,085,000	6,588,000	5,085,000	6,588,000	1.30
34	2001	Tabs	60	63,600	3,816,000	4,920,000	3,816,000	4,920,000	1.29
34	2001	Tabs	100	56,500	5,650,000	7,310,000	5,650,000	7,310,000	1.29
35	2001	Caps	20	5,200	104,000	259,000	104,000	259,000	2.49
35	2001	Caps	100	53,000	5,300,000	11,196,000	5,300,000	11,196,000	2.11
35	2001	Caps	1000	0	0	0	0	0	0.00
36	2001	Caps	20	11,100	222,000	464,000	222,000	464,000	2.09
36	2001	Caps	100	24,100	2,410,000	4,926,000	2,410,000	4,926,000	2.04
37	2001	Tabs	28	4,200	117,600	500,000	117,600	500,000	4.25
37	2001	Tabs	100	2,500	250,000	986,000	250,000	986,000	3.94
38	2001	Caps	100	5,500	550,000	1,730,000	550,000	1,730,000	3.15
39	2001	Caps	20	6,800	136,000	470,000	136,000	470,000	3.46
39	2001	Caps	100	11,200	1,120,000	3,746,000	1,120,000	3,746,000	3.34
40	2001	Caps	100	500	50,000	121,000	50,000	121,000	2.42
41	2001	Tabs	50	5,000	250,000	635,000	250,000	635,000	2.54
42	2001	Caps	100	4,000	400,000	500,000	400,000	500,000	1.25
42	2001	Caps	250	700	175,000	191,000	175,000	191,000	1.09
43	2001	Tabs	50	7,700	385,000	363,000	385,000	363,000	0.94

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
44	2001	Caps	20	31,800	636,000	453,000	636,000	453,000	0.71
44	2001	Caps	250	6,000	1,500,000	611,000	1,500,000	611,000	0.41
45	2001	Tabs	18	0	0	0	0	0	0.00
45	2001	Tabs	100	9,300	930,000	1,012,000	930,000	1,012,000	1.09
45	2001	Tabs	1000	1,800	1,800,000	1,908,000	1,800,000	1,908,000	1.06
46	2001	Caps	100	11,200	1,120,000	1,210,000	1,120,000	1,210,000	1.08
46	2001	Caps	500	500	250,000	276,000	250,000	276,000	1.10
47	2001	Caps	20	43,400	868,000	1,149,000	868,000	1,149,000	1.32
47	2001	Caps	100	13,200	1,320,000	1,715,000	1,320,000	1,715,000	1.30
48	2001	Tabs	100	8,400	840,000	1,813,000	840,000	1,813,000	2.16
49	2001	Tabs	20	5,500	110,000	44,000	110,000	44,000	0.40
49	2001	Tabs	100	600	60,000	17,000	60,000	17,000	0.28
49	2001	Tabs	1000	8,700	8,700,000	1,705,000	8,700,000	1,705,000	0.20
50	2001	Tabs	100	5,700	570,000	1,070,000	570,000	1,070,000	1.88
51	2001	Tabs	100	5,000	500,000	959,000	500,000	959,000	1.92
52	2001	Caps	100	400	40,000	21,000	40,000	21,000	0.53
52	2001	Caps	250	1,200	300,000	145,000	300,000	145,000	0.48
52	2001	Caps	500	3,300	1,650,000	792,000	1,650,000	792,000	0.48
53	2001	Tabs	60	3,700	222,000	757,000	222,000	757,000	3.41
54	2001	Caps	20	3,600	72,000	33,000	72,000	33,000	0.46
54	2001	Caps	100	5,900	590,000	194,000	590,000	194,000	0.33
54	2001	Caps	500	1,900	950,000	272,000	950,000	272,000	0.29
55	2001	Tabs	50	3,100	155,000	169,000	155,000	169,000	1.09
56	2001	Caps	100	2,900	290,000	127,000	290,000	127,000	0.44
57	2001	Tabs	30	2,400	72,000	107,000	72,000	107,000	1.49
57	2001	Tabs	100	400	40,000	53,000	40,000	53,000	1.33
58	2001	Caps	100	100	10,000	127,000	10,000	127,000	12.70
59	2001	Caps	50	100	5,000	12,000	5,000	12,000	2.40
60	2001	Tabs	20	38	760	3,000	760	3,000	3.95
61	2001	Tabs	10	113,000	1,130,000	1,341,000	1,130,000	1,341,000	1.19
61	2001	Tabs	18	1,344,800	24,206,400	27,074,000	24,206,400	27,074,000	1.12
61	2001	Tabs	54	62,500	3,375,000	3,629,000	3,375,000	3,629,000	1.08
61	2001	Tabs	100	288,300	28,830,000	29,884,000	28,830,000	29,884,000	1.04
62	2001	Tabs	20	92,600	1,852,000	1,037,000	1,852,000	1,037,000	0.56
62	2001	Tabs	100	95,400	9,540,000	4,420,000	9,540,000	4,420,000	0.46
62	2001	Tabs	500	189,500	94,750,000	35,540,000	94,750,000	35,540,000	0.38
63	2001	Tabs	10	0	0	0	0	0	0.00
63	2001	Tabs	12	19,800	237,600	127,000	237,600	127,000	0.53
63	2001	Tabs	20	5,500	110,000	41,000	110,000	41,000	0.37
63	2001	Tabs	24	485,800	11,659,200	5,699,000	11,659,200	5,699,000	0.49
63	2001	Tabs	50	238,500	11,925,000	4,281,000	11,925,000	4,281,000	0.36
63	2001	Tabs	100	500,300	50,030,000	15,138,000	50,030,000	15,138,000	0.30
64	2001	Caps	20	68,200	1,364,000	909,000	1,364,000	909,000	0.67
64	2001	Caps	30	3,200	96,000	51,000	96,000	51,000	0.53
65	2001	Tabs	18	810,800	14,594,400	16,569,000	14,594,400	16,569,000	1.14
65	2001	Tabs	54	35,800	1,933,200	2,091,000	1,933,200	2,091,000	1.08
65	2001	Tabs	100	108,500	10,850,000	11,348,000	10,850,000	11,348,000	1.05
65	2001	Tabs	1000	400	400,000	443,000	400,000	443,000	1.11
66	2001	Tabs	18	940,100	16,921,800	15,803,000	16,921,800	15,803,000	0.93
66	2001	Tabs	100	173,300	17,330,000	13,306,000	17,330,000	13,306,000	0.77
67	2001	Caps	30	407,700	12,231,000	14,703,000	12,231,000	14,703,000	1.20
67	2001	Caps	60	58,000	3,480,000	4,881,000	3,480,000	4,881,000	1.40
68	2001	Tabs	54	18,300	988,200	1,066,000	988,200	1,066,000	1.08
69	2001	Tabs	18	364,900	6,568,200	7,438,000	6,568,200	7,438,000	1.13

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
69	2001	Tabs	100	64,300	6,430,000	6,700,000	6,430,000	6,700,000	1.04
69	2001	Tabs	1000	400	400,000	394,000	400,000	394,000	0.99
70	2001	Tabs	12	344,500	4,134,000	3,933,000	4,134,000	3,933,000	0.95
70	2001	Tabs	24	235,200	5,644,800	4,706,000	5,644,800	4,706,000	0.83
70	2001	Tabs	48	71,200	3,417,600	2,565,000	3,417,600	2,565,000	0.75
70	2001	Tabs	96	50,100	4,809,600	3,302,000	4,809,600	3,302,000	0.69
71	2001	Tabs	18	14,800	266,400	201,000	266,400	201,000	0.75
71	2001	Tabs	100	154,200	15,420,000	6,464,000	15,420,000	6,464,000	0.42
71	2001	Tabs	500	47,600	23,800,000	7,915,000	23,800,000	7,915,000	0.33
72	2001	Tabs	12	134,900	1,618,800	696,000	1,618,800	696,000	0.43
72	2001	Tabs	24	97,400	2,337,600	962,000	2,337,600	962,000	0.41
72	2001	Tabs	48	13,100	628,800	251,000	628,800	251,000	0.40
72	2001	Tabs	72	36,000	2,592,000	868,000	2,592,000	868,000	0.33
72	2001	Tabs	96	1,800	172,800	21,000	172,800	21,000	0.12
73	2001	Tabs	12	274,400	3,292,800	867,000	3,292,800	867,000	0.26
73	2001	Tabs	24	165,400	3,969,600	1,103,000	3,969,600	1,103,000	0.28
73	2001	Tabs	48	94,800	4,550,400	1,248,000	4,550,400	1,248,000	0.27
73	2001	Tabs	96	81,600	7,833,600	1,942,000	7,833,600	1,942,000	0.25
73	2001	Tabs	1000	7,600	7,600,000	622,000	7,600,000	622,000	0.08
74	2001	Tabs	5000	1,200	6,000,000	693,000	6,000,000	693,000	0.12
75	2001	Tabs	10	38,700	387,000	132,000	387,000	132,000	0.34
75	2001	Tabs	38	22,100	839,800	217,000	839,800	217,000	0.26
75	2001	Tabs	76	20,200	1,535,200	312,000	1,535,200	312,000	0.20
76	2001	Tabs	96	0	0	0	0	0	0.00
77	2001	Tabs	18	8,600	154,800	127,000	154,800	127,000	0.82
77	2001	Tabs	100	19,300	1,930,000	1,554,000	1,930,000	1,554,000	0.81
77	2001	Tabs	500	11,200	5,600,000	4,543,000	5,600,000	4,543,000	0.81
78	2001	Tabs	20	293,500	5,870,000	5,239,000	5,870,000	5,239,000	0.89
79	2001	Tabs	20	11,100	222,000	254,000	222,000	254,000	1.14
79	2001	Tabs	500	30,600	15,300,000	3,823,000	15,300,000	3,823,000	0.25
80	2001	Tabs	10	116,000	1,160,000	952,000	1,160,000	952,000	0.82
80	2001	Tabs	30	62,900	1,887,000	1,399,000	1,887,000	1,399,000	0.74
80	2001	Tabs	60	29,900	1,794,000	1,185,000	1,794,000	1,185,000	0.66
80	2001	Tabs	500	1,900	950,000	445,000	950,000	445,000	0.47
81	2001	Tabs	20	29,800	596,000	355,000	596,000	355,000	0.60
81	2001	Tabs	100	9,800	980,000	527,000	980,000	527,000	0.54
81	2001	Tabs	500	10,900	5,450,000	3,074,000	5,450,000	3,074,000	0.56
82	2001	Tabs	1000	4,700	4,700,000	372,000	4,700,000	372,000	0.08
82	2001	Tabs	5000	4,100	20,500,000	284,000	20,500,000	284,000	0.01
83	2001	Tabs	10	10,100	101,000	26,000	101,000	26,000	0.26
83	2001	Tabs	20	7,400	148,000	29,000	148,000	29,000	0.20
83	2001	Tabs	100	38,400	3,840,000	356,000	3,840,000	356,000	0.09
83	2001	Tabs	1000	9,400	9,400,000	746,000	9,400,000	746,000	0.08
83	2001	Tabs	5000	7,100	35,500,000	488,000	35,500,000	488,000	0.01
84	2001	Tabs	100	5,800	580,000	506,000	580,000	506,000	0.87
85	2001	Caps	250	10,500	2,625,000	1,114,000	2,625,000	1,114,000	0.42
86	2001	Tabs	18	117,200	2,109,600	1,679,000	2,109,600	1,679,000	0.80
86	2001	Tabs	50	100	5,000	2,000	5,000	2,000	0.40
86	2001	Tabs	54	6,900	372,600	258,000	372,600	258,000	0.69
86	2001	Tabs	100	26,900	2,690,000	1,556,000	2,690,000	1,556,000	0.58
87	2001	Tabs	1000	9,000	9,000,000	3,067,000	9,000,000	3,067,000	0.34
87	2001	Tabs	5000	2,200	11,000,000	64,000	11,000,000	64,000	0.01
88	2001	Tabs	100	6,000	600,000	294,000	600,000	294,000	0.49
89	2001	Tabs	20	26,000	520,000	152,000	520,000	152,000	0.29

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
89	2001	Tabs	100	10,300	1,030,000	211,000	1,030,000	211,000	0.20
89	2001	Tabs	500	1,400	700,000	76,000	700,000	76,000	0.11
90	2001	Tabs	20	30,500	610,000	371,000	610,000	371,000	0.61
90	2001	Tabs	50	16,200	810,000	435,000	810,000	435,000	0.54
90	2001	Tabs	500	5,800	2,900,000	928,000	2,900,000	928,000	0.32
90	2001	Tabs	5000	200	1,000,000	58,000	1,000,000	58,000	0.06
91	2001	Tabs	20	14,600	292,000	155,000	292,000	155,000	0.53
91	2001	Tabs	100	10,600	1,060,000	447,000	1,060,000	447,000	0.42
91	2001	Tabs	500	9,200	4,600,000	1,427,000	4,600,000	1,427,000	0.31
92	2001	Tabs	20	74,400	1,488,000	175,000	1,488,000	175,000	0.12
93	2001	Tabs	5000	2,600	13,000,000	1,611,000	13,000,000	1,611,000	0.12
94	2001	Caplets	24	52,200	1,252,800	797,000	1,252,800	797,000	0.64
95	2001	Tabs	2	3,200	6,400	2,000	6,400	2,000	0.31
95	2001	Tabs	12	71,500	858,000	266,000	858,000	266,000	0.31
95	2001	Tabs	24	51,200	1,228,800	293,000	1,228,800	293,000	0.24
95	2001	Tabs	30	200	6,000	1,000	6,000	1,000	0.17
95	2001	Tabs	50	39,100	1,955,000	414,000	1,955,000	414,000	0.21
95	2001	Tabs	100	24,400	2,440,000	471,000	2,440,000	471,000	0.19
96	2001	Tabs	20	0	0	0	0	0	0.00
97	2001	Tabs	20	26,800	536,000	634,000	536,000	634,000	1.18
97	2001	Tabs	100	5,800	580,000	535,000	580,000	535,000	0.92
98	2001	Tabs	100	50	5,000	2,000	5,000	2,000	0.40
99	2001	Tabs	20	4,300	86,000	37,000	86,000	37,000	0.43
99	2001	Tabs	1000	3,700	3,700,000	809,000	3,700,000	809,000	0.22
99	2001	Tabs	5000	500	2,500,000	264,000	2,500,000	264,000	0.11
100	2001	Caps	18	9,700	174,600	76,000	174,600	76,000	0.44
100	2001	Caps	250	1,800	450,000	202,000	450,000	202,000	0.45
101	2001	Tabs	1000	200	200,000	6,000	200,000	6,000	0.03
101	2001	Tabs	5000	100	500,000	21,000	500,000	21,000	0.04
102	2001	Tabs	100	8,400	840,000	136,000	840,000	136,000	0.16
102	2001	Tabs	1000	6,900	6,900,000	561,000	6,900,000	561,000	0.08
102	2001	Tabs	5000	1,700	8,500,000	238,000	8,500,000	238,000	0.03
103	2001	Tabs	20	2,900	58,000	61,000	58,000	61,000	1.05
103	2001	Tabs	100	2,300	230,000	257,000	230,000	257,000	1.12
103	2001	Tabs	500	1,900	950,000	629,000	950,000	629,000	0.66
103	2001	Tabs	1000	20	20,000	2,000	20,000	2,000	0.10
104	2001	Tabs	1000	400	400,000	16,000	400,000	16,000	0.04
104	2001	Tabs	5000	1,000	5,000,000	442,000	5,000,000	442,000	0.09
105	2001	Tabs	30	22,100	663,000	856,000	663,000	856,000	1.29
106	2001	Tabs	20	15,600	312,000	290,000	312,000	290,000	0.93
106	2001	Tabs	100	5,800	580,000	490,000	580,000	490,000	0.84
106	2001	Tabs	1000	400	400,000	5,000	400,000	5,000	0.01
107	2001	Caps	18	16,700	300,600	392,000	300,600	392,000	1.30
107	2001	Caps	54	900	48,600	70,000	48,600	70,000	1.44
107	2001	Caps	100	2,200	220,000	308,000	220,000	308,000	1.40
108	2001	Tabs	20	35,700	714,000	739,000	714,000	739,000	1.04
109	2001	Tabs	20	4,300	86,000	100,000	86,000	100,000	1.16
109	2001	Tabs	100	3,600	360,000	386,000	360,000	386,000	1.07
110	2001	Tabs	10	11,900	119,000	56,000	119,000	56,000	0.47
110	2001	Tabs	30	16,700	501,000	155,000	501,000	155,000	0.31
111	2001	Tabs	10	15,200	152,000	47,000	152,000	47,000	0.31
111	2001	Tabs	20	27,300	546,000	160,000	546,000	160,000	0.29
111	2001	Tabs	50	16,000	800,000	196,000	800,000	196,000	0.25
111	2001	Tabs	100	8,400	840,000	85,000	840,000	85,000	0.10

Product number	Year	Dosage form	Pack size	Units	Number of dosage units	Rand Value	Adjusted Number of Dosage units	2001 Rand Value	Value per Tab/Cap
112	2001	Tabs	20	16,500	330,000	270,000	330,000	270,000	0.82
112	2001	Tabs	500	1,800	900,000	415,000	900,000	415,000	0.46
113	2001	Tabs	18	4,800	86,400	72,000	86,400	72,000	0.83
113	2001	Tabs	100	700	70,000	50,000	70,000	50,000	0.71
113	2001	Tabs	500	1,400	700,000	449,000	700,000	449,000	0.64
114	2001	Tabs	24	37,900	909,600	553,000	909,600	553,000	0.61
115	2001	Tabs	10	17,300	173,000	58,000	173,000	58,000	0.34
115	2001	Tabs	30	22,700	681,000	157,000	681,000	157,000	0.23
115	2001	Tabs	50	7,500	375,000	84,000	375,000	84,000	0.22
115	2001	Tabs	100	12,800	1,280,000	239,000	1,280,000	239,000	0.19
116	2001	Caps	12	23,800	285,600	245,000	285,600	245,000	0.86
116	2001	Caps	24	14,900	357,600	277,000	357,600	277,000	0.77
117	2001	Tabs	1000	1,900	1,900,000	278,000	1,900,000	278,000	0.15
118	2001	Caps	5000	1,800	9,000,000	212,000	9,000,000	212,000	0.02
119	2001	Tabs	20	15,300	306,000	273,000	306,000	273,000	0.89
120	2001	Tabs	20	8,400	168,000	74,000	168,000	74,000	0.44
120	2001	Tabs	24	1,600	38,400	16,000	38,400	16,000	0.42
120	2001	Tabs	50	1,400	70,000	27,000	70,000	27,000	0.39
120	2001	Tabs	100	3,500	350,000	113,000	350,000	113,000	0.32
121	2001	Caps	24	1,900	45,600	37,000	45,600	37,000	0.81
122	2001	Tabs	500	0	0	0	0	0	0.00
123	2001	Tabs	12	2,300	27,600	15,000	27,600	15,000	0.54
123	2001	Tabs	24	2,600	62,400	21,000	62,400	21,000	0.34
123	2001	Tabs	60	3,600	216,000	42,000	216,000	42,000	0.19
123	2001	Tabs	96	2,300	220,800	37,000	220,800	37,000	0.17
124	2001	Tabs	10	1,500	15,000	2,000	15,000	2,000	0.13
124	2001	Tabs	100	10,700	1,070,000	95,000	1,070,000	95,000	0.09
124	2001	Tabs	200	100	20,000	1,000	20,000	1,000	0.05
125	2001	Tabs	20	10,400	208,000	22,000	208,000	22,000	0.11
125	2001	Tabs	100	8,500	850,000	58,000	850,000	58,000	0.07
126	2001	Tabs	5000	0	0	0	0	0	0.00
127	2001	Tabs	100	400	40,000	4,000	40,000	4,000	0.10
127	2001	Tabs	1000	300	300,000	5,000	300,000	5,000	0.02
127	2001	Tabs	5000	500	2,500,000	43,000	2,500,000	43,000	0.02
128	2001	Tabs	20	1,500	30,000	11,000	30,000	11,000	0.37
129	2001	Tabs	1000	100	100,000	39,000	100,000	39,000	0.39
130	2001	Tabs	1000	1,200	1,200,000	38,000	1,200,000	38,000	0.03
131	2001	Tabs	30	1,200	36,000	37,000	36,000	37,000	1.03
132	2001	Tabs	1000	700	700,000	24,000	700,000	24,000	0.03
133	2001	Tabs	20	400	8,000	3,000	8,000	3,000	0.38
133	2001	Tabs	500	100	50,000	14,000	50,000	14,000	0.28
134	2001	Tabs	24	200	4,800	2,000	4,800	2,000	0.42
134	2001	Tabs	100	300	30,000	8,000	30,000	8,000	0.27
135	2001	Caps	20	300	6,000	7,000	6,000	7,000	1.17
136	2001	Tabs	30	600	18,000	7,000	18,000	7,000	0.39
137	2001	Tabs	100	100	10,000	1,000	10,000	1,000	0.10
137	2001	Tabs	500	100	50,000	4,000	50,000	4,000	0.08
138	2001	Tabs	500	30	15,000	3,000	15,000	3,000	0.20

Appendix D: Rand Value for Non-Narcotic Analgesics sold from 1992 to 2001

Year	Unadjusted Value (Rands)	Adjusted Value (Rands)
1992	213,986,500	398,349,474
1993	242,554,400	412,132,185
1994	275,187,300	425,557,602
1995	321,000,700	464,383,410
1996	368,805,300	487,766,679
1997	399,495,900	498,086,327
1998	466,608,600	533,659,535
1999	524,820,900	587,077,390
2000	569,666,000	595,386,473
2001	712,291,000	712,291,000

Appendix E: Sum of dosage units and Rand value for Meprobamate-containing analgesics from 1992 to 2001

Year	Total unadjusted dosage units	Value unadjusted	Total population adjusted dosage units	Value adjusted to 2001
1992	89,740,000	29,886,000	109,076,048	55,634,689
1993	81,128,000	28,870,500	96,494,299	49,054,819
1994	85,112,500	30,174,200	99,062,696	46,662,256
1995	91,623,500	32,445,300	104,353,857	46,937,776
1996	105,692,500	38,723,700	117,795,614	51,214,369
1997	109,323,000	38,983,500	119,228,069	48,604,124
1998	109,344,500	42,019,300	116,693,023	48,057,409
1999	109,921,200	43,514,700	114,792,060	48,676,599
2000	121,473,100	50,308,000	124,135,303	52,579,411
2001	169,827,500	76,348,000	169,827,500	76,348,000

Appendix F: Macro economic data

Year	CPI	Population mid-year	Population end-year	CPI growth factor	Population growth factor
1991	52.6	36,198,900	36,595,350	2.04	1.24
1992	57.6	36,991,800	37,397,000	1.86	1.22
1993	63.1	37,802,200	38,216,350	1.70	1.19
1994	69.3	38,630,500	39,053,800	1.55	1.16
1995	74.1	39,477,100	39,909,700	1.45	1.14
1996	81.1	40,342,300	40,784,500	1.32	1.11
1997	86.0	41,226,700	41,678,600	1.25	1.09
1998	93.7	42,130,500	42,592,403	1.14	1.07
1999	95.8	43,054,306	43,526,095	1.12	1.04
2000	102.6	43,997,884	44,480,012	1.05	1.02
2001	107.2	44,962,141	45,454,836	1.00	1.00