Prescription patterns of enzyme-containing products in South Africa over a 2-year period

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Enzymes are traded in five categories, namely medical (intervention), diagnostic (detection and quantification), molecular biology, biofuel and industrial. Therapeutic enzymes have been investigated for different uses, for example, for the treatment of genetic disorders, blood clotting disorders, cancer and infectious diseases and for burn debridement. No studies on the prescription of enzyme-containing products in South Africa could be found. Enzymes are classified in the *Monthly Index of Medical Specialities* under digestants, enzymes and fibrinolytics. The primary aim of this study was to investigate the prescription patterns and cost of enzyme-containing products in South Africa. A private health-care medicines claims database for 2010 and 2011 of approximately 4.5 million records was analysed retrospectively. Enzyme-containing products constituted a small percentage of medical insurance claims (only 0.02% of approximately 4.5 million claims for products and procedures), yet they were relatively expensive. A total of 906 products was prescribed at a cost of almost ZAR2 million over the 2 years. Hyaluronidase was the most frequently prescribed (60.04%), followed by pancreatin-containing products (34.66%). Pancreatin (lipase/protease/amylase) is primarily used in the management of pancreatic exocrine insufficiency. The average cost per hyaluronidase prescription paid by the medical insurance schemes was ZAR280. Other enzyme-containing products prescribed were imiglucerase, alteplase and tenecteplase. Imiglucerase was overall the most expensive. Alteplase, tenecteplase and streptokinase are antithrombotic enzymes that are used in the treatment of acute myocardial infarction or ischaemic stroke. Streptokinase, regarded as the most affordable antithrombotic enzyme, was not prescribed during the period under study. With the growing opportunities for enzymes for therapeutics, the use of enzyme-containing products which are comparatively expensive require cost-effectiveness studies.

Introduction

Enzymes are natural proteins that catalyse chemical reactions, converting a specific set of reactants (substrates) into specific products. Enzymes are highly specific and have several applications in different industries, such as the paper, starch, leather, pharmaceutical, baking, beer brewing, detergent, and wine-making industries.[1] Enzymes are traded in five distinct categories, namely medical (intervention), diagnostic (detection and quantification), molecular biology, biofuel and industrial. Based on their application, enzymes can be categorised into two major categories[1]: industrial enzymes and medical enzymes. The differences between industrial and medical enzymes are given in Table 1.

Table 1: Differences between industrial and medical enzymes[1]

Industrial enzymes	Medical enzymes
Produced in large quantities	Produced in small quantities
Partially purified but at an optimum	Extensively purified
Economic concerns are very important	Excellent functionality
Used as catalysts; hence, functionally, industrial enzymes are catalytic	Used to treat various diseases; hence, functionally, medical enzymes are therapeutic
Source of industrial enzymes is microbial and recombinant	Source of medical enzymes is mainly human or animal and recombinant

The market for enzymes in medicine is growing. The global market for industrial enzymes was valued at USD2.9 billion in 2008 and reached about USD3.1 billion in 2009.[1] In contrast to this, the global market for medical enzymes was estimated at USD6 billion in 2010, and it is growing to an estimated USD7.2 billion in 2015.[2] Therapeutic enzymes are the biggest segment in terms of revenue generated.[2] This sector was valued at USD5.3 billion in 2010 and is expected to increase to USD6.3 billion in 2015.[2]

The variety of enzymes and their potential therapeutic applications are considerable.[3] Some examples of enzymes which have realised the potential to become important therapeutic agents are asparaginase, hyaluronidase, ribonuclease, streptokinase and urokinase.[3] Enzymes as medicines (therapeutic enzymes) have two important features that distinguish them from all other types of medicines.[4] Firstly, enzymes often bind and act on their targets with great affinity and specificity, and, secondly, enzymes are catalytic and convert multiple target molecules to the desired products.[4] These two features make enzymes specific and potent medicines that can accomplish therapeutic biochemistry in the body that small molecules cannot. Enzymes can often be used for treatments complementary to those by small molecules, without one necessarily being better than the other. Each has its own

best application. These characteristics have resulted in the development of many enzyme-containing medicines for a wide range of disorders.

For the past 50 years, therapeutic enzymes have been investigated for the treatment of genetic disorders, blood clotting disorders, cancer and infectious diseases, as well as for burn debridement, amongst others, and have been registered as 'orphan drugs' or 'therapeutic interventions'.[4] The field has developed rapidly, and, in 1987, the US Federal Drug Administration approved the first recombinant enzyme drug alteplase, which is a human tissue plasminogen activator.[4] Even though products classified under 'Enzymes' in the *Monthly Index of Medical Specialities* (MIMS) [5] are reimbursed by medical aid insurance schemes in South Africa, no drug utilisation studies could be found in the literature on the prescription, usage patterns and cost of these products despite the fact that they are relatively expensive and deemed of national importance. MIMS[5] lists most of the pharmaceutical products in the South African market, especially those regularly prescribed, and is regarded as a standard reference source of available medicines in South Africa.

Enzyme-containing products are included in MIMS Category 27.0.0 (Enzymes), but are also referred to in MIMS Categories 8.3 (Fibrinolytics) and 12.1 (Digestants).[5] Only six enzyme active ingredients are listed in these categories – hyaluronidase, imiglucerase and pancreatin and three antithrombotic enzymes (alteplase, tenecteplase and streptokinase).[5,6] This list is limited, even though there are more types of enzymes used in therapeutics in other parts of the world, either as registered pharmaceuticals or as orphan drugs.[4]

Four of the six enzyme-containing products are prescription only (Schedule 4) medicines as classified in the *Medicines and Related Substances Act, No 101 of 1965* (as amended) in South Africa; the exceptions are hyaluronidase and pancreatin, which are Schedule 1 medicines (available over the counter in pharmacies).[5-7] All these products are for parenteral administration, except the pancreatin-containing products.

Hyaluronidase (hyaluronoglucosaminidase EC 3.2.1.35) is a glycosidase hydrolysing 1,4-linkages between *N*-acetyl-β-*D*-glucosamine.[8] The enzyme is extracted from ovine or bovine testes as the protein is present on the posterior head and the acrosomal membrane of mammalian sperm.[9] Recently, recombinant forms of hyaluronidase (produced by the combining of material from more than one origin), such as rHuPH20, have been introduced onto the market.[9,10] Hyaluronidase modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, which temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids or of localised transudates, thus facilitating their absorption. It is used as an adjunct to increase the absorption and dispersion of other injected drugs[10], for hypodermoclysis, for improved resorption of subcutaneously administered radiocontrast media in urography, for the effective decrease of injected depots of hyaluronic acid in aesthetic surgery[11], and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. It is used off-label for the treatment of vitreous haemorrhage and diabetic retinopathy. Sodium hyaluronate 10 mg/mL is included in the Standard Treatment Guidelines and Essential Medicines List for South Africa (Hospital Level Adults).[12] It is used as an ocular peri-operative pharmaceutical product and is classified under 'Surgical and diagnostic products' (Section 18.8).[12] It is therefore used in the public health sector in hospitals, but no data on the total number of prescriptions could be found.

Imiglucerase is a recombinant DNA-produced analogue of human β-glucocerebrosidase[4] (EC 3.2.1.45). The enzyme hydrolyses the beta glycosidic links in glucocerebroside that is an intermediate in lipid metabolism. A mutation in the glucocerebrosidase gene leads to the disorder known as Gaucher's disease (a lysosomal storage disease) that occurs in the absence of glucocerebrosidase activity. The use of glucocerebrosidase in enzyme replacement therapy is the first of its kind using an exogenous enzyme targeting its natural site of activity in the body.[4]

Pancreatin is an extract from ovine pancreas and contains lipases (pancreatic triacylglycerol lipase EC 3.1.1.3), α-amylase (EC 3.2.1.1), proteases (trypsin EC 3.4.21.4) and chymotrypsin (EC 3.2.21.1) in varying proportions. Pancreatin is used to treat pancreatic insufficiencies (both prescription and over-the-counter) as well as in the treatment of fat malabsorption in HIV patients and pancreatic insufficiency in cystic fibrosis patients (where the lipases are from recombinant maize[4]).

The antithrombotic enzymes are tissue plasminogen activators that are used to remove blockages in blood vessels in acute ischaemic strokes, myocardial infarctions and pulmonary oedemas. Alteplase and tenecteplase (EC 3.4.21.68) are serine proteases of human origin that cleave plasminogen to plasmin, which is the enzyme responsible for clot breakdown. Streptokinase (EC 3.4.24.29) produced by various strains of streptococci is able to bind and activate plasminogen in a non-proteolytic manner to break down fibrin clots.

In the light of the identification of medical enzymes as an important research focus for South African academia and industry, this study identified trends in the prescription of medical enzymes in South Africa. The primary aim of the study was to investigate the prescription patterns and cost of products classified as enzymes in a South African private health-care insurance claims database over a 2-year period.

Methodology

A retrospective, cross-sectional drug utilisation study was conducted on the database of a private medical insurance scheme administrator in South Africa. According to the South African Board of Healthcare Funders that represents 72 health insurers in South Africa, only 16% of the South African population is covered by medical insurance.[13] This figure equates to 3.5 million insured members and their 4.6 million dependants. The remainder of the South African population, that is 39.9 million people, is dependent on the government's medical services.

Data covered 2010 and 2011 and included medication, procedures and devices (a total of 2 126 264 records for 2010 at an amount claimed of ZAR173 812 440.86, and 2 298 312 records for 2011 at an amount claimed of ZAR169 127 258.13). Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity), price and various reimbursement variables.

MIMS[5] was used to identify and classify the medicines. All records for 'Enzymes' (MIMS Category 27.0.0 Enzymes (8.3; 12.1)) were extracted, as well as records in Categories 8.3 (Fibrinolytics) and 12.1 (Digestants).[5] Microsoft Access® and Excel® were used to analyse the data. Basic descriptive statistics were calculated. The cost indicated is the amount that was paid by the respective medical aid insurance schemes and may differ from the single exit price (SEP)[14] that is used in South Africa, as not all medical aid insurance schemes cover the full costs of these products and co-payments may have to be made by patients. At the time of the study (at the juncture between 2010 and 2011), EUR1.00 was equal to ZAR9.38, USD1.00 was equal to ZAR7.64 and GBP1.00 was equal to ZAR11.48.

Limitations of the study were that no clinical information or diagnoses were available in the database, and that only data of patients served by the private health-care sector in South Africa were included. Also, only products containing enzymes that were prescribed during 2010 and 2011 are discussed in the results section, although more trade name products have since become available on the South African market. Permission to conduct this study was obtained from the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University (ethics clearance number: H08-HEA-PHA-005).

Results and discussion

Enzyme-containing products constituted only 0.02% of the approximately 4.5 million claims for products and procedures paid for by the medical insurance schemes interrogated in this study, and 0.57% of cost. Of the enzyme-containing products available for prescription in South Africa,

only five were prescribed and submitted for reimbursement by the medical insurance company whose database was interrogated.

In the 2 years under study, a total of 906 products (525 in 2010 and 381 in 2011) were prescribed at a cost of ZAR1 956 948.76 with an average cost of ZAR2 159.99 (SD=R9 929.54) to 579 patients. The large standard deviation is because of the wide variation in cost between the different trade name products, with some products relatively inexpensive (the lowest average cost per product was ZAR82.34) and other products extremely expensive (the highest average cost per product was ZAR62 470.48). Patients were prescribed on average 1.56 (SD=1.65) products over the 2 years. The 579 patients identified included 292 female and 287 male patients. The average age of patients was 55.17 (SD=16.00) years (female: 55.53 (SD=17.71) years; male: 54.81 (SD=15.27) years). Nearly two-thirds of patients (64.59%) were between 40 and 69 years of age.

The different enzyme-containing product classes that were dispensed and paid for are given in Figure 1. Most products were prescribed in MIMS Category 27.0.0, accounting for 62.69% of the number of prescriptions for enzymes and 80.99% of the total amount claimed for enzymes over the 2 years. About half of the products (52.21%) were dispensed by private hospitals.

Only two enzyme-containing products were prescribed in MIMS Category 27.0.0[5], namely Cerezyme® (imiglucerase) powder for injection (200 units/mL and 400 units/mL) and Hyalase® injection (hyaluronidase 1500 iu/ampoule, 10 ampoules per package). Only 24 prescriptions were dispensed for imiglucerase (12 prescriptions for 200 units/mL in 2010 and 12 prescriptions for 400 units/mL in 2011) (see Table 2).

Hyaluronidase was the most frequently prescribed (60.04% of all enzyme products), followed by pancreatin-containing products (34.66%). A total of 544 prescriptions for hyaluronidase injections were dispensed (273 products in 2010 and 271 products in 2011) to 376 patients at a total cost of ZAR152 611.61 (average cost of ZAR286.85; SD=ZAR54.29). The average age of patients was 59.47 (SD=14.40) years. Nearly all the injections were dispensed in private hospitals or by unattached operating theatres (day clinics). Only two prescriptions for hyaluronidase were dispensed by ophthalmologists. Patients received an average of 1.45 (SD=0.61) prescriptions for hyaluronidase over the 2 years, with patients in the 50–59-year age group receiving the highest average of 1.52 prescriptions. The average cost per product paid by the medical aids was ZAR280.54 (ZAR279.22 in 2010 and ZAR281.86 in 2011). The SEP (unit price) on 12 January 2012 for hyaluronidase was ZAR283.40 (effective from 22 May 2010).[14]

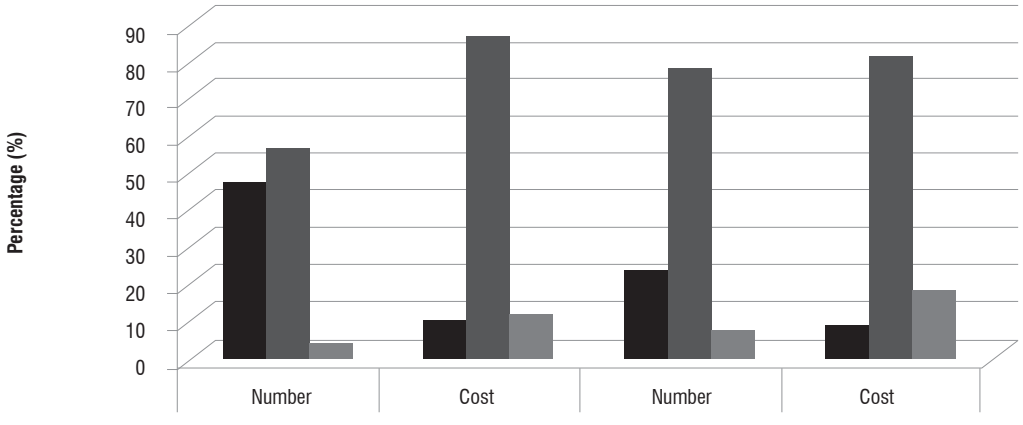
Hyaluronidase is classified in the Anatomical Therapeutic Chemical / Defined Daily Dose (ATC/DDD) Index as an enzyme under 'Blood and Blood Forming Organs (Other Haematological Agents)'.[6,15] It is used off-label for the treatment of vitreous haemorrhage and diabetic retinopathy. It is not possible to speculate on the reason for its use. Recently, it was reported that administering recombinant human hyaluronidase (rHuPH20) with meal-time insulin injections could help improve blood sugar control in people with type-1 diabetes (the combination led to smaller rises in glucose levels than treatment with insulin lispro alone).[16]

Imiglucerase was overall the most expensive (an average cost of ZAR58 103.26 for the 200 units/5 mL vials and ZAR62 470.48 for the 400 units/5 mL vials prescribed, and a total cost of ZAR697 239.17 for the 200 units/5 mL vial and ZAR749 645.73 for the 400 units/5 mL vial). Imiglucerase, used in the treatment of Gaucher's disease, is also listed in MIMS Category 26.0.0 (Biologicals)[5] and in ATC Group A16AB02.[6, 15]

Ten prescriptions were dispensed for alteplase at an average cost of ZAR6572.60 per prescription. Alteplase is used as fibrinolytic therapy in acute myocardial infarction within 6 h of symptom onset, as thrombolytic treatment in patients with acute massive pulmonary embolism and haemodynamic instability, as thrombolytic treatment of acute ischaemic stroke initially within 3 h after the onset of stroke symptoms and after the exclusion of intracranial haemorrhage.[5]

Tenecteplase, of which 14 injections were dispensed, is also used as thrombolytic therapy in acute myocardial infarction as soon as possible after symptom onset but within 6–9 h of symptom onset. The average amount claimed per injection was ZAR11905.72 for 8000 units and ZAR13091.24 for 10 000 units.

The pancreatin-containing products are available from pharmacies and are indicated as supplementation for pancreatic exocrine insufficiency caused by chronic pancreatitis, cystic fibrosis or partial pancreatectomy.[4] The formulation with dimethicone is used for abdominal distention due to cumulative gas and foam, in hepatic and biliary dysfunction and in post-operative flatulence and pre-gastrointestinal radiologic



	2010 Number	2010 Cost	2011 Number	2011 Cost
12.1.0 Digestant	44.76	7.25	20.73	6.20
27.0.0 Enzymes	53.71	83.85	75.07	78.50
8.3.0 Fibrinolytics	1.52	8.90	4.20	15.30

Figure 1: Number of products and amount claimed (in ZAR) of the different classes of enzyme-containing products as a percentage of the total number and the total cost of all enzyme-containing products (n=906).

Table 2: Number of enzyme active ingredients and total amount claimed for each enzyme active ingredient

Active ingredients	Number		Both years		Amount claimed (in ZAR)		Both years		SEP (in ZAR) (unit price)†
	2010	2011	Number	%	2010	2011	Amount	%	
12.1.10 Digestants									
Pancreatin 170 mg and dimethicone 80 mg tablets (100 tablets)	34	2	36	3.97	3491.27	77.84	3569.11	0.18	3.01
Pancreatin 170 mg and dimethicone 80 mg tablets (25 tablets)	163	10	173	19.09	12990.68	1253.39	14244.07	0.73	3.01
Pancreatin capsules - enzyme activity per capsule amylase 8000, lipase 10 000, protease 600 Ph Eur units (100 capsules)	30	47	77	8.50	8 939.75	16 886.69	25 826.44	1.32	5.69
Pancreatin capsules - enzyme activity per capsule amylase 18 000, lipase 25 000, protease 1000 PIP units (100 capsules)	8	20	28	3.09	29 689.96	38 675.92	68 365.88	3.49	13.68
27.0.0 Enzymes									
Hyaluronidase 1500 iu/ampoule injection (10 injections)	270	274	544	60.04	74 156.62	78 454.99	152 611.61	7.80	283.40
Imiglucerase powder for injection vial (200 units/5 mL)	12	0	12	1.32	697 239.17	0	697 239.17	35.63	1 534.90
Imiglucerase powder for injection vial (400 units/5 mL)	0	12	12	1.32	0	749 645.73	749 645.73	38.31	1 534.90
8.3.0 Fibrinolytics									
Alteplase in 2333 mg dry solvent (50 mg vial + solvent kit)	3	7	10	1.10	17 318.85	48 407.10	65 725.95	3.36	6 050.89
Tenecteplase vial (8000 units) injection	1	2	3	0.33	11 346.37	24 370.78	35 717.15	1.83	12 185.39
Tenecteplase vial (10 000 units) injection	4	7	11	1.21	51 926.23	92 077.42	144 003.65	7.36	13 579.34

†Single exit price (SEP)[14] as on 12 January 2012.

examination preparation.[5] These products were mostly dispensed by pharmacies and in private hospitals and were relatively inexpensive.

In the database being interrogated, no prescriptions were encountered for streptokinase, which is indicated for severe myocardial infarction and is regarded as the most affordable antithrombotic enzyme.[6] In the SEP file of January 2012,[14] streptokinase was indicated as 'not approved' and it was not prescribed during the period under study.

Conclusion and recommendations

No studies could be found in the literature on the prescription patterns of enzyme-containing products in South Africa. Therefore, the aim of this study was to investigate these patterns as well as the cost of enzyme-containing products in South Africa using a private medical insurance scheme database. A limitation of this study was the absence of diagnoses in the database, which did not allow for the determination of the reason for the use of the various enzyme-containing products.

Considering the increased emphasis on therapeutic enzymes and the growing global market for enzymes, it is noteworthy that medical enzymes only constituted 0.02% of reimbursements from the medical claims database. Whilst it may be difficult to speculate on the underlying reasons, both cost and familiarity with enzymes may play a role in the prescription patterns found. Medicinal products containing enzymes are relatively expensive and warrant further studies into their cost-effectiveness. Only one trade name product was prescribed for each enzyme-containing product in this study (although some trade names had more than one dosage strength or pack size). It will be interesting to monitor how prescription patterns and cost will be affected when more trade name products are introduced. In the absence of other drug utilisation studies with which to compare the results, this study can be regarded as a baseline study and further studies are recommended.

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