

South African National Essential Medicines List Adult Hospital Level Medication Review Process: International Price Comparison Component: Dermatology

Date:	31st October 2017
Medication:	Tretinoin topical
Indication:	Acne Vulgaris

Authors: This document was prepared by Ravikanthi Rapiti, Alexander Winch and Thomas Wilkinson

Background

The Essential Drugs Programme (EDP) of the Affordable Medicines Directorate (AMD) requested a price comparison of tretinoin for the Adult Hospital Level Dermatology component to be reviewed by the National Essential Medicines List Committee (NEMLC). This document provides information on the pricing of tretinoin formulations in South Africa and internationally utilising publicly available information and provides brief analysis on global supply.

Medicine Overview

In South Africa, topical retinoids such as tretinoin are indicated for non-inflammatory acne where benzoyl peroxide alone is ineffective¹.

Tretinoin (ATC code D10AD01²) gel and cream are manufactured in a 0.025% gel and a 0.05% cream formulation and distributed internationally through a variety of brand names including RETIN-A, AiroI, Stieva, Smooderm, AVITA®, Retacnyl and ILOTYCIN-A.

The name of the active ingredient tretinoin is derived from all-trans-retinoic acid. Tretinoin is an endogenous retinoid metabolite of Vitamin A that binds to intracellular receptors in the cytosol and nucleus.

International Price Analysis

The South African Rand (ZAR) equivalent benchmark prices were primarily sought for Australia, Canada, New Zealand and Spain, initially against the generic name “tretinoin” and all associated brand names discussed above. Of these four countries, prices were found for Canada and New Zealand. Australia and Spain had no publicly available price data.

¹ Adult Hospital Level Standard Treatment Guidelines 2015_v5.0 South Africa

² www.whocc.no/atc_ddd_index

Prices for tretinoin were then sourced for countries utilising the WHO national medicine price database³. Of the rest of the countries on the WHO national medicine price database, prices were additionally found for the United Kingdom. These prices were then converted into ZAR, using the conversion rates⁴ found on 2nd October 2017 from raw prices and an average price over a 12 month period November 2016-November 2017 was calculated as indicated by the “Price in Rand”, in Table 1.

Tretinoin combination therapies, and/or non-topical preparations were excluded from price analysis. All brands, where non-inflammatory acne was not indicated as the primary use, tretinoin combination therapies, or non-topical preparations, and any mode of delivery that was not a cream or gel were excluded from price analysis.

³ http://www.who.int/medicines/areas/access/sources_prices/national_medicine_price_sources.pdf

⁴ <https://www.oanda.com/currency/average>

Table 1: International price comparison for tretinoin 0.05% cream and tretinoin 0.025% gel

Country	Manufacturer	Brand Name	Originator/ Generic	Active Ingredient	Dispensing type	Price	Price in Rand	Price Type	Source	Last Updated
South Africa	Janssen Pharmaceuticals Pty (Ltd)	RETIN-A	Originator	Tretinoin 0.025%	20g gel	R 44.60	R 44.60	Public - Delivered incl. VAT	Contract circular HP08-2017SSP	effective 05/2017 - 2020
Canada	Stiefel Canada Inc.	Stieva-A	Originator	Tretinoin 0.025%	20g gel	CAN\$ 0.3022	R 3.29	Public MOHTC reimbursement rate	https://www.formulary.health.gov.on.ca/formulary/detail.xhtml?drugId=00587966	10/4/2016
United Kingdom	Janssen Pharmaceuticals Pty (Ltd)	RETIN-A	Originator	Tretinoin 0.025%	60g gel	GBP 5.28	R 95.36	NHS Reimbursement rate	Expert interview - http://www.drugtariff.nhsbsa.nhs.uk/#/00475250-DA_1/DA00475244/Home	November 2016

Country	Manufacturer	Brand Name	Originator/ Generic	Active Ingredient	Dispensing type	Price	Price in Rand	Price Type	Source	Last Updated
South Africa	Janssen Pharmaceuticals Pty (Ltd)	RETIN-A	Originator	Tretinoin 0.05%	20g cream	R32.49	R 32.49	Public - Delivered incl. VAT	Contract circular HP08-2017SSP	effective 05/2017 - 2020
Canada	Stiefel Canada Inc.	Stieva-A	Originator	Tretinoin 0.05%	20g cream	CAN\$ 0.21	R 2.28	Public MOHTC reimbursement	https://www.formulary.health.gov.on.ca/formulary/detail.xhtml?drugId=00518182	10/4/2016
New Zealand	Bausch & Lomb (NZ) Ltd	ReTrieve	Originator	Tretinoin 0.05%	50g cream	NZ\$ 13.90	R 134.25	Manufacturers price	http://www.pharmac.govt.nz/healthpros/PharmaceuticalSchedule/Schedule?osq=Tretinoin&code=C1001012286	Effective 10/2017
United Kingdom	Janssen Pharmaceuticals	RETINOVA	Originator	Tretinoin 0.05%	20g gel	GBP 13.75	R 248.33	NHS Reimbursement rate	Expert interview - http://www.drugtariff.nhsbsa.nhs.uk/#/00475250-DA_1/DA00475244/Home	Discontinued Nov 2016

Market analysis of local Medicines Control Council (MCC) registered products

According to the South African 2015 database of medicine prices⁵, four tretinoin 0.05% 20g creams are registered for use through the Medicines Control Council (MCC). These are branded RETIN-A, AiroI, Retacnyl and ILOTYCIN-A, which are manufactured and distributed by Janssen Pharmaceuticals Pty (Ltd), Pharmaco Distribution (Pty) Ltd, Galderma Laboratories and Pharmacare Limited respectively. The 0.025% 20g tretinoin gel is registered with the MCC under the brand name RETIN-A and manufactured by Janssen Pharmaceuticals Pty (Ltd)⁶.

In the South African public sector, according to Contract Note HP08-2017SSP⁷, brand name RETIN-A is procured in the formulations 0.05% 20g cream and 0.025% 20g gel, at R32.49 and R44.60 respectively inclusive of 14% VAT. This contract is effective 1st May 2017 - 30th June 2020. Janssen Pharmaceuticals Pty (Ltd) is currently the sole tender supplier and given the current landscape of tretinoin purchased with a discontinuation of these products in other contexts, the impact of a potential discontinuation of tretinoin by the manufacturer or distributor in South Africa is a possibility.

Table 2: MCC registered products and related public sector prices of tretinoin 0.05% cream and 0.025%gel

Proprietary Name	Active Ingredients	Strength	Dosage Form	Pack Size	Manufacturer Price (ZAR)	SEP (ZAR)	Unit Price (ZAR)	Effective Date	Originator or Generic	Public Sector Delivered price incl. 14% VAT (ZAR)
Retin A	Tretinoin	0.05%	CRM	20	208.59	269.13	13.46	07 April 2015	Originator	32.49
Retin A	Tretinoin	0.025%	GEL	20	208.74	269.33	13.47	07 April 2015	Originator	44.6002
Ilotycin A	Tretinoin	0.05%	CRM	20	76.87	103.08	5.15	24 March 2015	Generic	
AiroI®	Tretinoin	0.05%	CRE	20	85.05	102.04	5.10	07 April 2014	Originator	
Retacnyl	Tretinoin	0.05%	CRM	30	228.84	292.19	9.74	13 April 2015	Originator	

Adapalene 0.1% cream and gel is also available in the South African private sector, under the brand names Differin, Epiduo and Deriva, and manufactured by Galderma Laboratories and Glenmark Pharmaceuticals Ltd.

⁵ <http://www.health.gov.za/index.php/single-exit-price-documents>

⁶ South African Database of Medicine Prices, National Department of Health, 26th March 2015

⁷ http://www.health.gov.za/tender/docs/HP08-2017SSP_Contract_Circular_20170504.pdf

Table 3: MCC registered products for Adapalene 0.1% cream and gel

Proprietary Name	Active Ingredients	Strength	Dosage Form	Pack Size	Manufacturer Price (ZAR)	SEP (ZAR)	Unit Price (ZAR)	Effective Date	Originator or Generic	Public Sector Delivered price incl. 14% VAT (ZAR)
Differin Gel	Adapalene	0.1%	JEL	30	163.19	208.35	6.95	28 March 2014	Originator	58.16
Differin	Adapalene	0.1%	CRM	30	162.70	207.74	6.92	28 March 2014	Originator	
Deriva Gel	Adapalene	0.1%	JEL	30	125.43	156.27	5.21	22 September 2014	Generic	
Epiduo 0,1 % / 2,5 %	Adapalene	0.1%	Gel	30	174.07	222.23	7.41	13 April 2015	Originator	

For price comparison of Adapalene, the UK⁸ and New Zealand⁹ reimbursement rates in the public sector respectively are R309.23 and R224.14 for Differin.

Active Pharmaceutical Ingredient(API) Global Supply Analysis

There is a lack of market information regarding the use of tretinoin in public sector health systems internationally, which is also reflected in the lack price information that was sourced. The demand for continued international supply of tretinoin will be influenced by recommendations of national institutions and professional societies.

European Dermatology Forum clinical guidelines for Acne¹⁰, most recently updated in 2016, state that adapalene shows the best tolerability/ safety profile, followed by isotretinoin and then tretinoin, and that patient preference is for adapalene over tretinoin. The UK recommends the use of topical retinoids for non-inflammatory acne, such as adapalene, or oral administered isotretinoin alone or in combination¹¹, whilst tretinoin 0.05% cream or 0.025% gel is not specifically mentioned in the guidance. In many European health systems, the UK and Australia, tretinoin 0.05% cream and 0.025% gel appears

⁸ <http://www.pharmac.govt.nz/2010/07/30/2010-07-30%20Proposal%20for%20a%20topical%20anti-acne%20treatments.pdf>

⁹ <https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff>

¹⁰ S3-Guideline for the Treatment of Acne (Update 2016) Developed by the Guideline Subcommittee "Acne" of the European Dermatology Forum

¹¹ <http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/lambeth-borough-prescribing-committee/Lambeth%20Borough%20Prescribing%20Committee/Clinical%20Guidelines/Management%20of%20Acne%20Guidelines%20Jan%202015.pdf>

to have been discontinued by the manufacturer and distributor of the products in 2012¹², and 2010 respectively.

The American Academy of Dermatology in 2007¹³ noted that, ‘there is no current consensus of the relative efficacy of available topical retinoids (tretinoin, adapalene, tazarotene, and isotretinoin). This is supported by US guidelines developed in 2016¹⁴, which recommend that topical adapalene, tretinoin and benzoyl peroxide can all be safely used in the management of preadolescent acne in children. Tretinoin topical preparations are available in the USA, however, consistent pricing or supply information was not able to be sourced for this report.

A review of the Active Pharmaceutical Ingredient (API) sources, indicated that there currently is five producers of tretinoin of which 3 producers are in Europe and 2 producers are in India¹⁵. Table 4 provides with the name of the producers retrieved from reviewing the API sources.

Table 4: API Sources

Country	Producer
Germany	BASF SE Ludwigshafen
India	Biophore India Pharmaceuticals Pvt. Ltd.
India	USV Ltd.
Italy	OLON S.p.A.
Switzerland	DSM Nutritional Products Ltd. Kaiseraugst

Limitations

This report provides a brief overview of international pricing and supply and market analysis of MCC tretinoin products in South Africa. As the report relies on publically-available data, it was not possible to provide current pricing on products beyond United Kingdom, Canada, and New Zealand. In addition, current pricing data was not available for countries where tretinoin has been discontinued. The API search conducted only found 5 producers of tretinoin globally.

This document was prepared for the Essential Drugs Program, by Supply Chain Technical Assistance program funded by USAID: PRICELESS SA under the. No conflicts of interest are declared by the contributing authors.

¹²Expert interview with NHS worker

¹³ Strauss, John S., Daniel P. Krowchuk, James J. Leyden, Anne W. Lucky, Alan R. Shalita, Elaine C. Siegfried, Diane M. Thiboutot et al. "Guidelines of care for acne vulgaris management." *Journal of the American Academy of Dermatology* 56, no. 4 (2007): 651-663.

¹⁴ [http://www.jaad.org/article/S0190-9622\(15\)02614-6/pdf](http://www.jaad.org/article/S0190-9622(15)02614-6/pdf)

¹⁵ API Sourcing Database. Retrieved from <https://www.apisourcing.net/database/?api=Tretinoin&query=Tretinoin>. Accessed 6 November 2017