

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug Use Data
Paracalcitol (Zemplar®, NDA 20-819)
Pediatric Exclusivity Grant Date: December 8, 2003

****This document contains proprietary data from IMS Health and Premier which cannot be shared outside of FDA without clearance from IMS Health and Premier obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines the drug use for Zemplar® (paracalcitol) in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on December 8, 2003. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The IMS Health, National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution. It was clear from these data that the majority of this product was sold into non-retail settings; 99.6% of all vials sold were to non-retail pharmacies during year 2004, of which 88% were sold to clinics. Since the Agency does not have access to data describing the use of drug products in clinics, we could

only examine the utilization patterns for paricalcitol focusing on the inpatient setting. Inpatient use was assessed from hospital billing data provided by Premier™. *It should be noted, however, that the inpatient use described in the current study likely reflects only 10-11% of the total sales of paricalcitol.*

There was an overall increase in the sale of injectable vitamin D analogues (USC5 76340) from 16 million vials sold in year 2002 to nearly 29.5 million vials sold in year 2004. Paricalcitol had the highest market share in all three years surveyed with 89.2% or 14.4 million vials sold in 2002 to 76.3% or 18.2 million vials sold in 2003 and to 73.4% or 21.6 million vials sold in 2004. Although the percent market share for paricalcitol declined over the years, the number of vials sold increased 26.6% between years 2002 and 2003, and 18.6% between years 2003 and 2004.

Overall, the inpatient use of paricalcitol appears to have increased over the two year study period from 60,933 projected discharges during October 1, 2002 to September 31, 2003, to 79,830 projected discharges during October 1, 2003 to September 31, 2004. Use of paricalcitol is primarily in the adult population. Pediatric use (patient ages 0-16) was captured only during the post-exclusivity period fourth quarter of 2003 over the two year time period surveyed with approximately 84 projected discharges. In adults (ages 17 and greater) and children (ages 0-16), “hemodialysis” (ICD-9 39.95) was the most common procedural diagnosis associated with the discharges in which paricalcitol was billed. This represented approximately 42% of actual discharges and 57-64% of projected discharges during the 2-year time period.

In the subset of 37 pediatric hospitals, the use of paricalcitol in the pediatric population (ages 0-16) was sporadic at best. A total of 3 discharges were captured during the fourth quarter of 2003 and also during the third quarter of 2002. In both time periods, the use appeared to be in only the 10-14 year age range. The only principal procedural diagnosis associated with paricalcitol in both time periods was “hemodialysis”.

Looking to other data sources, we examined information collected by the U.S. Renal Data System (USRDS) for all patients in the U.S. with end-stage renal disease (ESRD), which suggests that 70% of all dialysis units use intravenous vitamin D products. As of the end of 2002, paricalcitol was used by five times as many patients in these centers as calcitriol; doxercalciferol was used only marginally. Of the 308,910 patients on dialysis in December 2002, 2,347 of them were aged 0-19 years and approximately 45-50% were given an injectable vitamin D product, most likely paricalcitol. It is not clear, however, how many of these patients were treated in outpatient clinics as opposed to the inpatient setting.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that act requires the reporting of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events

associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Zemplar® (paricalcitol injection 5 mcg/mL) NDA 20-819 is a synthetic vitamin D analog used for the treatment and prevention of secondary hyperparathyroidism associated with chronic renal failure. It is estimated that approximately 50% of patients undergoing dialysis are affected by secondary hyperparathyroidism.¹

Zemplar® was approved on April 17, 1998, and is available as a sterile aqueous solution for intravenous injection in 1 and 2 mL single-dose Fliptop Vials. It is administered as a bolus dose no more frequently than every other day at any time during dialysis. The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Zemplar® Extended-release Tablets (NDA 20-819/S-014) on December 8, 2003.

This review describes only inpatient drug use patterns for Zemplar® in the pediatric population as well as in the adult population in the years prior to and subsequent to the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

A. Determining Setting of Use

IMS Health, National Sales Perspectives™ data were used to determine the setting in which the product was sold. Sales of this product by number of vials or eaches sold from the manufacturer to various retail and non-retail channels of distribution were analyzed (Table 1). It was clear from these data that the majority of this product was sold into non-retail settings; 99.6% of all vials sold were to non-retail pharmacies during year 2004, of which 88% were sold to clinics. Since the Agency does not have access to data describing the use of drug products in clinics, we could only examine the utilization patterns for paricalcitol focusing on the inpatient setting. A major limitation of the current analysis is that the data resources available to the Agency do not capture use in the outpatient clinic setting. Inpatient use was assessed from hospital billing data provided by Premier™. *It should be noted, however, that the inpatient use described in the current study likely reflects only 10-11% of the total sales of paricalcitol.*

Table 1. Sale of Zemplar® Vials (Eaches) Sold to U.S. Distribution Channels, IMS Health, National Sales Perspectives™, 2004

U.S. Distribution Channels	Vials (Eaches)	%
Total	21,626,100	100.0
Retail Distribution Channel	91,800	0.4
Non-Retail Distribution Channel	21,534,400	99.6
Clinics	18,991,500	88.2
Non-Federal Hospitals	2,291,900	10.6

IMS Health, National Sales Perspectives™, Year 2004, Extracted March 2005. Original File: 0503zem3.dvr.

We examined the sales and inpatient drug use patterns for paricalcitol and other injectable vitamin D analogues to compare Zemplar® use relative to other products of the same therapeutic class. The injectable vitamin D products include paricalcitol, doxercalciferol, calcitriol, and ergocalciferol.

B. Data Resources

IMS HEALTH, NATIONAL SALES PERSPECTIVES™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS Health, National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, vials, and market share. These data are based on national projections.

For this analysis, the sales trend for paricalcitol was examined from January 2002 to December 2004, inclusive.

PREMIER™

Premier maintains a large hospital drug utilization and financial database which contains billing information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database. Data are available from January 2000 through the present, but have a lag time of approximately 6 months.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, we believe that most estimates of national inpatient drug use using Premier data appear to be reasonable, but strongly recommend making this determination on a drug-specific basis. We used projected estimates for paricalcitol, given its highly specific indication, limited types of setting of use, and single route of administration.

For this analysis, the total number of projected discharges associated with paricalcitol within Premier hospitals was examined for the time period from October 1, 2002 to September 31, 2004, inclusive.

PREMIER PEDIATRIC™

Premier's pediatric database is a subset of the larger database described above. Information is available from 37 pediatric hospitals. Data are also available from January 2000 through the present, but have a lag time of approximately six months.

For this analysis, the total number of distinct discharges associated with paricalcitol use within these 37 children's hospitals are examined from October 1, 2002 to September 31, 2004, inclusive.

RESULTS

I. Sales and Market Share

There was a substantive overall increase in the estimated sale of injectable vitamin D analogues (USC5 76340) from 16 million vials sold in year 2002 to nearly 29.5 million vials sold in year 2004 (Table 2). This represented an 82.5% increase from year 2002 to year 2004. Paricalcitol had the highest market share in all three years surveyed with 89.2% (14.4 million vials) in 2002, 76.3% (18.2 million vials) in 2003, and 73.4% (21.6 million vials) in 2004. Although the percent market share for paricalcitol declined over the years, the number of vials sold increased 26.6% between years 2002 and 2003, and 18.6% between years 2003 and 2004.

Table 2: Total Number of Vials (Eaches) Sold (in thousands) for Zemplar® and Other Injectable Vitamin D Analogues in the U.S., IMS Health, National Sales Perspectives™, Retail and Non-Retail, 2002 - 2004

	2002		2003		2004	
	Vials (000)	%	Vials (000)	%	Vials (000)	%
Total Injectable Vitamin D Analogues	16,154	100.0	23,911	100.0	29,474	100.0
Paricalcitol	14,410.9	89.2	18,248	76.3	21,645	73.4
Doxercalciferol	712.7	4.4	2,488.8	10.4	5,589.5	19
Calcitriol	1,021.2	6.3	3,166.3	13.2	2,237.5	7.6
Ergocalciferol	9.6	0.1	8.2	0	2.4	0

IMS Health, National Sales Perspectives™, Year 2004, Extracted March 2005. Original File: 0503zem4.dvr

II. Inpatient Use and Demographics

Acute Care Hospitals

Overall, the use of paricalcitol appears to have increased over the two year study period from 60,933 projected discharges during October 1, 2002 to September 31, 2003, to 79,830 projected discharges during October 1, 2003 to September 31, 2004. Use of paricalcitol is primarily in the adult population. Over the two-year time period surveyed, pediatric use (patient ages 0-16) was captured only during the post-exclusivity period fourth quarter of 2003 with approximately 84 projected discharges. In adults (ages 17 and greater) and children (ages 0-16), “hemodialysis” (ICD-9 39.95) was the most common procedural diagnosis associated with the discharges in which paricalcitol was billed. This represented approximately 42% of actual discharges and 57-64% of projected discharges during the 2-year time period (calculated from Table 3).

Table 3: Total Number of Projected Discharges Associated with Paricalcitol by Age Groups in Premier Hospitals, October 2002 through September 2004 (Rx Market Advisor™)

Patient Age Custom Groups	Principal Proc ICD9	October 2003 - September 2004		October 2002 - September 2003	
		Actual Discharges	Projected Discharges	Actual Discharges	Projected Discharges
Total		11,786	79,830	9,543	60,933
Patient Age 0-16	Total	9	84	0	0
Patient Age 0-16	39.95 Hemodialysis	4	54	0	0
Patient Age 0-16	None No principal procedural ICD-9	5	31	0	0
Patient Age 17 and Above	Total	11,777	79,746	9,543	60,933
Patient Age 17 and Above	39.95 Hemodialysis	4,999	45,803	3,999	35,071
Patient Age 17 and Above	None All other procedural ICD-9	6,778	33,945	5,544	25,862

Premier Rx Market Advisor, data extracted March 2005.

Pediatric Care Centers

In the subset of 37 pediatric hospitals, the use of paricalcitol in the pediatric population (ages 0-16) was sporadic. A total of 3 discharges were captured during the fourth quarter of 2003 and also during the third quarter of 2002. In both time periods, the use appeared to be in only the 10-14 year age range. The only principal procedural diagnosis associated with paricalcitol in both time periods was “hemodialysis” (ICD-9 39.95).

Table 4: Total Number of Discharges Associated with Paricalcitol by Age Groups in Premier Pediatric Hospitals, October 2002 through September 2004 (Rx Market Advisor™)

				2003 Q4	2002 Q3
	Age Grouping	ICD-9	Principal Procedural Diagnosis	Discharges	Discharges
Total				3	3
Paricalcitol	10-14	39.95	Hemodialysis	3	3

Premier Pediatric Rx Market Advisor, data extracted March 2005.

DISCUSSION

Based on sales data and data reflecting inpatient use, it appears that the use of Zemplar® is on the rise over the past three years, 2002 to 2004. Currently, however, much kidney dialysis treatment in the U.S. is provided in outpatient clinics; according to the United States Renal Data System (USRDS), the number of dialysis clinic centers, nationally, was 4,204 at the end of year 2002.¹ Sales data suggest that inpatient use represents only 10-11% of total product use. A major limitation of the current analysis is that the data resources available to the Agency do not capture use of paricalcitol in the outpatient clinic setting.

Looking to other data sources, we examined information collected by the USRDS for all patients in the U.S. with end-stage renal disease (ESRD).¹ The most recent data available are from the end of calendar year 2002, and suggest that 70% of all dialysis units use intravenous vitamin D products, with use more evident in freestanding centers relative to those units based in hospitals. As of the end of 2002, paricalcitol was used by five times as many patients in these centers as calcitriol; doxercalciferol was used only marginally. Of the 308,910 patients on dialysis in December 2002, 2,347 of them were aged 0-19 years and approximately 45-50% were given an injectable vitamin D product, most likely paricalcitol. It was not possible from these data, however, to determine which children were treated in outpatient vs. inpatient dialysis centers.

The limitations of sales data should be borne in mind when considering this analysis. The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of

distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

CONCLUSION

There was a substantial overall increase in the sale of injectable vitamin D analogues (USC5 76340) from 16 million vials sold in year 2002 to nearly 29.5 million vials sold in year 2004. Paricalcitol had the highest market share in all three years surveyed with 89.2% or 14.4 million vials sold in 2002 to 76.3% or 18.2 million vials sold in 2003 and to 73.4% or 21.6 million vials sold in 2004. Although the percent market share for paricalcitol declined over the years, the number of vials sold increased 26.6% between years 2002 and 2003, and 18.6% between years 2003 and 2004.

In the inpatient setting, the use of paricalcitol appears to have increased over the two year study period from 60,933 projected discharges during October 1, 2002 to September 31, 2003, to 79,830 projected discharges during October 1, 2003 to September 31, 2004. Use of paricalcitol is primarily in the adult population. Pediatric use (patient ages 0-16) was captured only during the post-exclusivity period fourth quarter of 2003 over the two year time period surveyed with approximately 84 projected discharges. In adults (ages 17 and greater) and children (ages 0-16), "hemodialysis" (ICD-9 39.95) was the most common procedural diagnosis associated with the discharges in which paricalcitol was billed. This represented approximately 42% of actual discharges and 57-64% of projected discharges during the 2-year time period.

In the subset of 37 pediatric hospitals, the use of paricalcitol in the pediatric population (ages 0-16) was sporadic at best. A total of 3 discharges were captured during the fourth quarter of 2003 and also during the third quarter of 2002. In both time periods, the use appeared to be in only the 10-14 year age range. The only principal procedural diagnosis associated with paricalcitol in both time periods was "hemodialysis" (ICD-9 39.93).

A major limitation of the current analysis is that the data resources available to the Agency do not capture use of paricalcitol in the outpatient clinic setting. However, based on data from USRDS, there could be as many as 1000 children undergoing dialysis who may be exposed to paricalcitol, but it is not clear whether they are treated in outpatient clinics or as inpatients.

Reference:

1. U.S. Renal Data System. 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States [on-line]. Available from URL: <http://www.usrds.org/> (Accessed 2005 March 16).

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