

Memorandum

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SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data
Anagrelide (Agraylin[®]) capsules (NDA 20-333)

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

EXECUTIVE SUMMARY

This consult examines drug utilization trends for anagrelide (Agraylin[®]) in the pediatric population (ages 1-16 years), with a primary focus on patterns of use one-year before and one-year following the granting of Pediatric Exclusivity on May 25, 2004. Proprietary drug use databases licensed by the Agency were used to determine the various retail and non-retail channels of distribution. The sales of anagrelide rose by 11% from the pre- to post-exclusivity years with 20 million and 22 million capsules sold, respectively. The majority of this product was sold into retail settings; 91% of all capsules sold were to retail pharmacies each year during 2002-2005, a third of which were sold to chain stores (data not shown). Outpatient drug utilization patterns were examined for the 3-year period from June 1, 2002 to May 31, 2005, with a primary focus on changes that may have occurred between the year preceding exclusivity (June 2003-May 2004) and the year following granting of exclusivity (June 2004-May 2005).

Total dispensed prescriptions for anagrelide appear to have remained steady between the pre- and post-exclusivity period. Among pediatric patients ages 0-16 years, the total number of anagrelide prescriptions dispensed decreased by 28% from approximately 339 in the pre-

exclusivity year to an estimated 245 prescriptions dispensed in the post-exclusivity year; this change should be interpreted with caution, however, due to the imprecision and variability of these small numbers. Prescriptions of anagrelide for pediatric patients aged 0-16 years old accounted for substantially less than 1% of dispensing in each of the three years of this analysis.

Oncology and Hematology were the most frequent specialties prescribing anagrelide from June 2002 - May 2005. Pediatricians ranked 10th in prescribing anagrelide during the post-exclusivity year and accounted for less than 0.5% of dispensed prescriptions in each of the three years in this analysis. The distribution of provider specialties prescribing anagrelide in the outpatient retail pharmacy settings showed no substantial change during the 36-month analysis period.

The most common diagnosis associated with a mention of anagrelide for adults and pediatric patients during office-based physician patient encounters was “Neoplasm, Other lymphatic and hematopoietic tissues” (ICD-9 code 238.7) followed by “Unspecified Diseases of blood and blood-forming organs” (ICD-9 code 289.9) which accounted for 43% and 38% of mentions, respectively, during the post-exclusivity period (June 2004 - May 2005).

In summary, dispensed prescriptions for anagrelide in the pediatric and adult population appears to have remained steady between the pre- and post-exclusivity period and pediatric patients accounted substantially less than 1% of the anagrelide prescriptions dispensed during each of the 3 years of this analysis.

INTRODUCTION

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the FDA to analyze the reports of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric 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.

Agrylin[®] (anagrelide), NDA 20-333, was approved on March 14, 1997, for the treatment of thrombocytopenia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events. Current practice guidelines recommend the use of hydroxyurea as the first line agent for patients at high risk for thrombotic or hemorrhagic complications.¹ However, there may be a risk of developing leukemia secondary to long term use of hydroxyurea in children and in young adults.^{2,3} Anagrelide has not been shown to have any leukemogenic or mutagenic potential.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Agrylin[®] on May 25, 2004. On December 10, 2004, Agrylin[®] (anagrelide), NDA 20-333/SE5-008 was approved for use in the pediatric population ages 7 through 14 years based on an open label pharmacokinetic (PK) and pharmacodynamic (PD) study.

This review describes outpatient drug usage of Agrylin[®] capsules in the pediatric population as compared to the adult population using interferon alpha and hydroxyurea as comparator products. Several outpatient data resources were used to examine the use of anagrelide by describing dispensed prescriptions, prescriber specialty, patient demographics and indications for use. Descriptions of the data sources used are given in the appendix. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

Determining Setting of Use

IMS Health, National Sales Perspectives[™] data (see Appendix for details on this data resource) were used to determine the setting in which the product was sold. Sales of this product by number of capsules sold by the manufacturer to various retail and non-retail channels of distribution were analyzed from June 2002 through May 2005. The sales of anagrelide have increased 11% from the pre- to post-exclusivity years, beginning with close to 20 million capsules sold from June 2003 to May 2004 to over 22 million capsules sold from June 2004 to May 2005 (data not shown). The majority of anagrelide was sold into retail settings; 91% of all capsules sold were into retail pharmacies during each of the three years (data not shown). A generic formulation of anagrelide entered the market in August of 2004 and accounted for 6% of the combined brand and generic anagrelide market during the post-exclusivity year.

RESULTS

I. Dispensed Prescriptions

Dispensed prescriptions for anagrelide decreased from 128,000 during June 2002 – May 2003 to 124,600 during the pre-exclusivity year; a decline of 2.6% (Table 1). Dispensed prescriptions then held steady at 124,400 during the post-exclusivity year. Generic anagrelide entered the market in August 2004 and accounted for approximately 4,336 prescriptions dispensed during the post-exclusivity period, or 3% of the total anagrelide market.

Compared to other agents used to treat thrombocytopenia, anagrelide held approximately 18% of the market share in terms of dispensed prescriptions. The majority of dispensed prescriptions were for hydroxyurea with 53% followed by interferon alpha with 29% of the market share during the post-exclusivity period.

Table 1: Total number of prescriptions dispensed* in retail pharmacies nationwide for anagrelide and selected other agents to treat thrombocytopenia During June 2002 – May 2005

| | June 2002 – May 2003 | | June 2003 – May 2004 | | June 2004 – May 2005 | |
|-------------------------|----------------------|-------------|----------------------|-------------|----------------------|-------------|
| | N [†] | (%) | N | (%) | N | (%) |
| Total | 852,307 | 100% | 727,987 | 100% | 684,345 | 100% |
| Anagrelide | 127,781 | 15% | 124,566 | 17% | 124,380 | 18% |
| Agrylin | 127,781 | 100% | 124,566 | 100% | 120,050 | 97% |
| Anagrelide | -- | -- | -- | -- | 4,336 | 3% |
| Interferon alpha | 341,663 | 40% | 256,960 | 35% | 199,224 | 29% |
| Hydroxyurea | 382,863 | 45% | 346,461 | 48% | 360,735 | 53% |

Verispan, LLC, June 2002 – May 2005, Data Extracted 8-2005 (File: D040346 0509 anagrelide TRx.qry)
[†] Subtotals may not sum exactly due to rounding error
* Does not include mail order prescriptions

Prescriber Specialty

Oncologists were the most frequent prescribers of anagrelide, accounting for nearly 40% of the total number of prescriptions dispensed during the three-year time period (Table 2). Hematologists ranked second in prescribing, accounting for an estimated 33% of dispensed prescriptions for anagrelide. Pediatricians ranked 10th in prescribing anagrelide, accounting for less than 0.5% of dispensed anagrelide prescriptions in each of the three years surveyed in this analysis. The distribution of provider specialties prescribing anagrelide in the outpatient retail pharmacy settings showed no substantial change during the 36-month study period.

Table 2: Total Number of Prescriptions Dispensed for Anagrelide Nationwide by Physician Specialty During June 2002 – May 2005

| | June 2002 – May 2003 | | June 2003 – May 2004 | | June 2004 – May 2005 | |
|-----------------------------|----------------------|--------|----------------------|--------|----------------------|--------|
| | N [†] | (%) | N [†] | (%) | N [†] | (%) |
| Anagrelide | 127,776 | 100.0% | 124,568 | 100.0% | 124,371 | 100.0% |
| Oncology | 50,887 | 39.8% | 48,508 | 38.9% | 46,813 | 37.6% |
| Hematology | 40,874 | 32.0% | 40,134 | 32.2% | 41,314 | 33.2% |
| Internal Medicine | 15,042 | 11.8% | 14,765 | 11.9% | 14,669 | 11.8% |
| Unspecified | 9,539 | 7.5% | 9,498 | 7.6% | 10,141 | 8.2% |
| GP/FM/DO* | 4,541 | 3.6% | 4,234 | 3.4% | 4,500 | 3.6% |
| Nurse Practitioners | 880 | 0.7% | 1,176 | 0.9% | 1,555 | 1.3% |
| Hospitalists | 1,121 | 0.9% | 1,511 | 1.2% | 1,404 | 1.1% |
| Cardiology | 410 | 0.3% | 408 | 0.3% | 412 | 0.3% |
| Physician Assistants | 377 | 0.3% | 425 | 0.3% | 386 | 0.3% |
| Pediatricians | 456 | 0.4% | 352 | 0.3% | 202 | 0.2% |
| All Others | 3,649 | 2.9% | 3,557 | 2.9% | 2,975 | 2.4% |

Verispan, LLC, June 2002 – May 2005, Data Extracted 8-2005 (File: D040346 0509 Anagrelide MDs.qry)
* General Practice, Family Medicine & Osteopathic physicians
[†] Subtotals may not sum exactly due to rounding error

II. Patient Demographics

The total number of anagrelide prescriptions (brand and generic combined) dispensed to pediatric patients ages 0-16 years old peaked in the pre-exclusivity year with approximately 339 prescriptions (Table 3). This decreased during the post-exclusivity year to 245 prescriptions. Dispensed prescriptions of anagrelide for pediatric patients aged 0-16 years old accounted for substantially less than 1% of total dispensed anagrelide prescriptions during the time periods before and after pediatric exclusivity was granted. Use of anagrelide in pediatric patients was so low as to make a pediatric subgroup analysis infeasible.

Table 3. Percentage of Anagrelide Prescriptions Dispensed* to Adult and Pediatric Patients by Retail Pharmacies During June 2002 – May 2005

| | June 2002 – May 2003 | | June 2003 – May 2004 | | June 2004 – May 2005 | |
|---------------------------|----------------------|--------|----------------------|--------|----------------------|--------|
| | N [†] | % | N [†] | % | N [†] | % |
| Anagrelide | 127,780 | 100.0% | 124,574 | 100.0% | 124,380 | 100.0% |
| 0-16 Years | 244 | 0.2% | 339 | 0.3% | 245 | 0.2% |
| 17 Years and Older | 127,446 | 99.7% | 123,567 | 99.2% | 123,363 | 99.2% |
| Age Unspecified | 90 | 0.1 | 668 | 0.5% | 772 | 0.6% |

Verispan, LLC, June 2002 – May 2005, Data Extracted 9-2005 (File: D040346 0509 Anagrelide Age 0-16.qry)
[†]Subtotals may not sum exactly due to rounding error
 *Does not include mail order prescriptions

III. Indications for Use

The most common diagnosis associated with a mention of anagrelide for all patients combined during office-based physician-patient encounters during the post-exclusivity year was “Neoplasm, Other lymphatic and hematopoietic tissues “ (ICD-9 code 238.7) followed by “Unspecified Diseases of blood and blood-forming organs” (ICD-9 code 289.9) , which accounted for 43% and 38% of mentions, respectively, during the post-exclusivity period of May 2004 - April 2005 (Table 4). Because use in the pediatric population was infrequent analysis of pediatric diagnoses was not performed.

Table 4: Top Diagnoses (in thousands) Associated with Projected Mentions of Agrylin[®] (anagrelide) for Pediatric and Adult Patients May 2002 - April 2005

| IMS Reported ICD-9 Code | May 2002 – April 2003 | | May 2003 – April 2004 | | May 2004 – April 2005 | |
|--|-----------------------|-----|-----------------------|-----|-----------------------|-----|
| | N (000) | (%) | N (000) | (%) | N (000) | (%) |
| Total Mentions | 174 | | 152 | | 175 | |
| 238.7 Neoplasm, Other lymphatic and hematopoietic tissues | 58 | 33% | 47 | 31% | 76 | 43% |
| 289.9 Unspec. Diseases of blood and blood-forming organs | 86 | 50% | 50 | 33% | 67 | 38% |
| 238.4 Polycythemia vera | 24 | 14% | 35 | 23% | 17 | 10% |
| Total Others (6) | 6 | 3% | 20 | 13% | 16 | 9% |

IMS National Disease and Therapeutic Index™ CD-ROM, NDTI 3yr. May 2002-April 2005. Data extracted 09-2005 (File: D040346 0509 Anagrelide Diags.xls)

LIMITATIONS

Myeloproliferative disorders are uncommon in pediatric patients. Findings from this consult should be interpreted in the context of the known limitations of use in the pediatric population and the databases used.

Sales data

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 product 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.

Outpatient use data

As with sales data, prescription data of the other recommended thrombocythemia therapies are included as comparators for anagrelide. Each of the comparator products are used for a wide variety of diseases, therefore direct comparisons must be made with this in mind. Interferon is used to treat several different cancers and hepatitis B while hydroxyurea is used as a chemotherapeutic agent, in HIV treatment, and for sickle cell anemia. Use of anagrelide in the pediatric population was very infrequent, resulting in imprecise and variable national estimates. Therefore, the apparently large drop in pediatric prescriptions between the pre- and post-exclusivity years may be due to a large amount of variation around these estimates rather than actual changes in prescribing patterns.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable as well, particularly when use is not common in the pediatric population, as in the case of anagrelide.

CONCLUSION

In summary, dispensed prescriptions for anagrelide in the pediatric and adult population appear to have remained steady between the pre- and post-exclusivity periods. In each year of this analysis, pediatric prescriptions accounted for substantially less than 1% of anagrelide dispensing.

APPENDIX

IMS HEALTH, IMS 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 of anagrelide was examined from June 1, 2002 – May 31, 2005 inclusive.

VERISPAN, LLC

Vector One™: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One™ receives over 1.8 billion prescription claims, representing over 150 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

Data for this analysis included prescriptions dispensed for anagrelide and selected other agents to treat thrombocythemia from June 1, 2002 – May 31, 2005 inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of anagrelide during office-based physician visits during the time period from June 1, 2002 – May 31, 2005 inclusive.

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¹ Barbui T., Barosi G., Grossi A., Gugliotta L., Liberato L., Marchetti M., Mazzucconi M., Rodeghiero F., Tura S., Practice Guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation; *Haematologica* Feb 2004; 89 (2): 215-232

² Cheung, M.C., Hicks, L.K. & Pendergrast, J. (2004). Thrombocytosis. *New England Journal of Medicine*, 350, 2524-25

³ Dame C., Sutor AH., Primary and Secondary Thrombocytosis in Childhood; *British Journal of Haematology*, 129, 165-177