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Review of Request for Orphan-Drug Designation

Application number:	12-3735
Date received:	June 6, 2012
Date assigned:	June 18, 2012
Date completed:	June 29, 2012
Date revised:	July 12, 2012
Generic name:	Mercaptopurine oral suspension
Trade name:	Xaluprine
Proposed orphan indication:	Treatment of acute lymphoblastic leukemia (ALL) in pediatric patients
Sponsor name and address:	Nova Laboratories Limited Martin House Gloucester Crescent Wigston, Leicester, England LE18 4YL
U.S. contact name and address:	Carol S. Auletta, DABT Director, Program Management Huntington Life Sciences Princeton Research Center PO Box 2360 Mettlers Road, East Millstone NJ 08875 Telephone: 732-873-2550 ext 2960 Email: aulettac@princeton.huntingdon.com
Regulatory status:	Mercaptopurine (trade name Purinethol) is approved in the United States for maintenance therapy of ALL as part of a combination regimen. Only for Children Pharmaceuticals was granted orphan designation for mercaptopurine oral liquid for the treatment of ALL in pediatric patients in December 2009.
Manufacturer:	(b) (4) [redacted]
Related orphan designation:	There are four active designations for ALL.

1.0 DESCRIPTION OF ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia or acute lymphocytic leukemia (ALL) is a disease in which too many immature lymphocytes exist in the blood and bone marrow. The cause of ALL is unknown in most patients; however, an increased risk for developing ALL is seen in certain

genetic conditions and in patients with a history of prior chemotherapy or radiation therapy. Early signs of ALL can be similar to those of the flu or other common diseases, such as fever, weakness, aching joints and bones and swollen lymph nodes. Acute lymphocytic leukemia is diagnosed by bone marrow biopsy.

Acute lymphocytic leukemia accounts for 23% of all childhood cancers. The prognosis of children with ALL is quite good, with about 75-85% free of recurrence at least 5 years after diagnosis with current therapy. In comparison to children with ALL, adults have a far poorer outcome and have a median survival of about 3 years. Successful treatment of adults with ALL includes systemically administered combination chemotherapy (vincristine, prednisone, L-asparaginase, cyclophosphamide, methotrexate, and 6-mercatopurine) with central nervous system (CNS) preventive therapy.

2.0 SCIENTIFIC RATIONALE

Mercaptopurine is FDA approved as a tablet formulation for the treatment of ALL. The sponsor is developing an oral liquid formulation of the product for use in pediatric ALL patients. The sponsor claims that their proposed oral liquid formulation offers more flexibility and accuracy in terms of dosing and improved ease of administration (and hence compliance) for children. There are also exceptional safety issues concerning the preparation of drugs for pediatric oncology. Splitting tablet doses, by cutting or crushing, exposes both the care givers and the home environment to cytotoxic contamination. It is widely recognized that this is common practice. Moreover, it has been demonstrated that splitting 50 mg Purinethol tablets into pieces results in poor accuracy of dosing, ranging from 54 to 159% of the desired tablet mass. This was the case even if commercially available tablet splitters were applied by a pharmacist experienced in the preparation of extemporaneous formulations (Breitkeutz et al., 2007). The sponsor also claims that medication errors have also been reported, including administration and prescribing errors, in children with ALL receiving mercaptopurine in an outpatient setting (Taylor JA et al., 2011).

Reviewer's comments: *The approval by the FDA of mercaptopurine (MP) tablets for the treatment of ALL provides a more than adequate scientific rationale. The issue with this application then becomes whether an oral liquid formulation is clinically superior (i.e., safer or more efficacious) than the approved tablet formulation or a major contribution to patient care. As noted in the November 30, 2009 review of application 09-2863 for another oral liquid formulation of MP for ALL, there are significant safety issues associated with the use of MP for the treatment of ALL and these safety issues can be compounded when the tablets are manipulated in order to dose pediatric patients. It is certainly feasible that parents attempting to prepare a dose of MP could accidentally over or underdose their child with serious consequences. Consequently, an oral liquid formulation of MP would be a "safer" product than the approved tablet formulation by eliminating the need for compounding procedures and thus reducing or avoiding potential serious medication errors. Therefore, for purposes of orphan designation, the sponsor has provided a plausible hypothesis for expecting an oral liquid formulation of MP to be a safer product than the approved tablet formulation of the drug.*

3.0 PREVALENCE ESTIMATE

The application contained a prevalence estimate of 15,000 pediatric ALL patients who would be candidates for treatment with MP.

Reviewer's comments: *The sponsor's prevalence estimate appears to be based more on the annual number of pediatric patients diagnosed with ALL rather than the number of patients alive with ALL who would be candidates for treatment with MP. However, the NCI SEER program lists the complete prevalence of ALL as 66,194 so the prevalence of this application is less than 200,000.*

4.0 REVIEWER'S EVALUATION AND RECOMMENDATION

In this application, Nova Laboratories Limited requests orphan-drug designation of mercaptopurine oral suspension for the treatment of ALL in pediatric patients. A tablet formulation of MP is approved for ALL but the safety issues associated with the use of MP are compounded when the tablets are manipulated in order to dose pediatric patients. As noted above, the sponsor has provided a plausible hypothesis for expecting an oral liquid formulation of MP to be a safer product than the approved tablet formulation. The prevalence figure for this application is 66,194.

Therefore, it is recommended that the sponsor's request for orphan designation of mercaptopurine oral suspension (trade name Xaluprine) for the treatment of ALL in pediatric patients be granted. The reference to the active moiety in the designation letter should be deleted from the designation letter. Additionally, the following paragraph should be included in the designation letter:

a plausible hypothesis (b)

> Please note that mercaptopurine oral suspension was granted orphan-product designation on the basis that it is clinically superior pursuant to 21 CFR 316.3(a)(3)(ii). In order to obtain market exclusivity for your product when a New Drug Application (NDA) for mercaptopurine oral suspension is approved, clinical studies submitted with the NDA need to provide evidence that mercaptopurine oral suspension is safer and comparable in efficacy to the approved formulation of mercaptopurine tablets.

Peter L. Vaccari, R.Ph.
OPD Contractor

Concurrence:

Date: 7/18/2012

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

cc:
HF-35/Designation file #12-3735

HF-35/Chron File

References

Breitkeutz J, Buckham J, Fischer R et al. Comparative in vitro studies on different 6-mercaptopurine formulations for use in children. Paediatric and Perinatal Drug Therapy 2007; 8(1).

Taylor JA, Winter L, Geyer LJ et al. Oral Outpatient Chemotherapy Medication Errors in Children With Acute Lymphoblastic Leukemia. Cancer 2006; 107: 1400–6.