

ADDENDUM- CLINICAL REVIEW

Application Type	Pediatric efficacy supplement for NDA 204412 (Delzicol)
Application Number(s)	sNDA 204412/3
Priority or Standard	Standard
Submit Date(s)	September 12, 2013
Received Date(s)	September 12, 2013
PDUFA Goal Date	July 12, 2014
Division / Office	DGIEP
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer Anil Rajpal, MD, Team Leader
Review Completion Date	February 13, 2014
Addendum Completion Date	April 1, 2014
Established Name	Mesalamine
(Proposed) Trade Name	Delzicol
Therapeutic Class	5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid)
Applicant	Warner Chilcott
Formulation(s)	400 mg delayed release tablets
Dosing Regimen	1.2 g/day to (b)(4) g/day twice daily oral
Indication(s)	Mildly to moderately active ulcerative colitis
Intended Population(s)	Pediatric patients ages 12 -17 years old

ADDENDUM TO CLINICAL REVIEW

This is a brief addendum to the clinical review for sNDA 204412/3, dated 2/14/2014, by Dr. Juli Tomaino. From a clinical perspective, sNDA 204412/3 is acceptable to support recommendation for approval of Delzicol 400 mg for the treatment of mildly to moderately active ulcerative colitis in patients ages 12 years and older, after agreement with revised labeling for Delzicol. As stated in Section 8 Post-Market Experience of the clinical review, a review of the postmarketing updates (Periodic Adverse Drug Experience (ADE) Reports) for Delzicol revealed multiple reports of patients having difficulty swallowing the medication. Based on the postmarketing reports of difficulty swallowing Delzicol, an Information Request (IR) was sent to the sponsor on February 18, 2014, requesting descriptions of any adverse events related to difficulty swallowing. On March 3, 2014, the sponsor responded to the IR and included a summary of the requested information and narrative descriptions from patient reports that were related to difficulty swallowing. Many of the reports included narrative descriptions that patients were experiencing the Delzicol capsule “melting,” “sticking” or “dissolving” in their mouth, or “do not slide down,” and “hard to swallow and gets stuck.” In addition, patients reported opening the capsule to remove the outer coating and swallowing the inner tablet without difficulty. Of note,

only one of the 49 cases of difficulty swallowing Delzicol were reported as a serious adverse event. Please refer to the sponsor’s Response to the Agency Information Request – AE for Difficulty Swallowing, dated March 3, 2014, for further details.

The following is a summary of the sponsor’s response:

- Complaints of difficulty swallowing the Asacol 400 mg tablet were not recorded in clinical trials for treatment of active ulcerative colitis (C3, C7, C14), maintenance of remission of UC (87086) or open-label compassionate use in inflammatory bowel disease (C12, C13)
- Complaints of difficulty swallowing the test product (Asacol tablets, 400 mg or 800 mg) were not recorded in Asacol 800 mg pivotal clinical trials 2000082, 2000083, or 2006444 (ASCEND I-III)
- Complaints of difficulty swallowing the test product (Delzicol capsule or Asacol 400 mg tablet) were not recorded in the Delzicol relative bioavailability study (PR-08210)
- 49 postmarketing cases were identified to be related to product swallowing difficulties
 - o 40 female patients, 8 male patients, 1 gender was not specified
 - o Of the 32 cases where age was provided, the mean age was 65.1 years and ranged from 44 to 88 years of age
 - o Of the 35 cases where the indication for use was provided, 24 cases listed ulcerative colitis, 9 cases listed Crohn’s, and 2 cases listed “other colitides” as the indication for use
 - o 2 patients reported pre-existing conditions that may have contributed to difficulty swallowing (1 patient reported a history of dysphagia, 1 patient reported a history of polio and diaphragm hemiparalysis)
 - o Reports of swallowing difficulty were generally consistent in describing the difficulty swallowing as related to the Delzicol capsule size, stickiness and dissolution

The table below provides a summary of the trend in number of patient reports of swallowing difficulty since the release of Delzicol in April 2013. The complaints increased in the first months when patients were switching from Asacol to Delzicol. Overall, complaints have decreased since July 2013.

Table 1: Number of Patient Complaints Related to Difficulty Swallowing Delzicol

Month / Year	No. of Complaints
4/13	2
5/13	8
6/13	4
7/13	11
8/13	8
9/13	5
10/13	6
11/13	1
12/13	2
1/14	2

(source: sponsor’s response to IR for Delzicol sNDA 204412/3, dated March 3, 2014, page 1/3)

For comparison, information on postmarket reports of difficulty swallowing Asacol and Asacol HD were requested. Both Asacol and Asacol HD revealed fewer reports of swallowing difficulties compared to Delzicol (see table below). Seven cases of swallowing difficulty were

identified for Asacol HD, one patient reporting difficulty with both Asacol HD and Delzicol, and 1 patient reported a pre-existing condition that could have contributed to dysphagia (neck cancer hospice patient with dysphagia/ aphagia). Eleven reports were identified for Asacol and five patients reported pre-existing conditions that may have contributed to dysphagia. For Asacol, patient age was reported for eight cases; four pediatric patients ages 8 to 11 years of age and four adult patients ages 18 to 93 years of age. In pediatric patients, the Asacol tablet was cut/crushed for children who had swallowing difficulties. A comparison of reports for Delzicol, Asacol, and Asacol HD is below.

Table 2: Summary of Reports Related to Swallowing Difficulty for Delzicol, Asacol, and Asacol HD

SOC	HLGT	HLT	PT	Delzicol (49 cases)	Asacol (11 cases)	Asacol HD (7 cases)
Injury, poisoning and procedural complications	Injuries NEC	Non-site specific injuries NEC	Foreign body	25	2	1
	Medication errors	Maladministrations	Wrong technique in drug usage process	10	1	2
			Drug administration error	0	3	1
General disorders and administration site conditions	Product quality issues	Product physical issues	Product size issue	17	0	2
			Product physical issue	10	0	0
			Capsule physical issue	4	0	0
			Product solubility abnormal	3	0	0
			Product coating issue	1	0	0
	Product quality issues NEC	Product quality issue	2	0	0	
	General system disorders NEC	Feelings and sensations NEC	Sensation of foreign body	1	0	0
Pain and discomfort NEC			1	0	0	
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Upper respiratory tract signs and symptoms	Choking	7	0	3
			Oropharyngeal pain	1	0	0
			Throat irritation	1	0	0
		Coughing and associated symptoms	Cough	0	0	1
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Retching	5	0	3
			Regurgitation	3	0	0
		Gastrointestinal signs and symptoms NEC	Dysphagia	3	6	3
	Gastrointestinal inflammatory conditions	Oesophagitis (excl infective)	Oesophageal irritation	1	0	0
	Gastrointestinal motility and defaecation conditions	Gastrointestinal atonic and hypomotility disorders NEC	Gastrooesophageal reflux disease	0	1	0

(source: sponsor's response to IR for Delzicol sNDA 204412/3, dated March 3, 2014, page 3/3)

The Division of Pharmacovigilance I (DPV I) performed an internal search of the FAERS database for reports related to difficulty swallowing Delzicol. DPV I's search of the FAERS database and review of periodic reports from Warner-Chilcott LLC, since the approval of Delzicol on February 1, 2013, identified 57 unique cases where the patient had difficulty swallowing the drug (n=53) or removing the outer capsule before swallowing (n=13). Among the 13 cases that reported removing outer capsules, nine documented the patient was having difficulty swallowing the capsule. The mean and median ages for the cases of swallowing difficulty were 62.6 years and 63 years, respectively, and ranged from 37 to 88 years (n=37). There were no pediatric reports. Please refer to the memo by Christian Cao, DPV I, for additional details.

Recommendations

This reviewer is in agreement with the recommendations by DPV I:

- Update the current Delzicol label to clearly inform patients not to open the capsule before swallowing
- Request that the sponsor submit 15-day alert reports for events of pill dysphagia or opening Delzicol capsules before swallowing regardless of event outcome to allow timely evaluation of these issues, particularly in the pediatric patients

In addition, this reviewer recommends revising the Delzicol label to include a statement that children should be assessed for the ability to swallow capsules. For final labeling agreements, see the updated label for Delzicol.

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/s/

JULI A TOMAINO
04/07/2014

ANIL K RAJPAL
04/07/2014
I concur with Dr. Tomaino.