FOI 23/194 – Debendox studies and hospitals/universities involved

REQUEST
14 March 2023

Please could you provide the eleven independent studies that were conducted for the morning sickness drug Debendox.

I would also like to know how many of the Hospitals and Universities that were involved in these studies that were conducted in the UK and USA were funded by Merrell Dow Pharmaceuticals.

MHRA RESPONSE
17 May 2023

Debendox was first available as a triple combination product of doxylamine succinate (an antihistamine), pyridoxine hydrochloride (vitamin B6), and dicyclomine hydrochloride (an antispasmodic). Following a US Food and Drug Administration (FDA) retrospective review of the efficacy of each multi-ingredient medication marketed between 1938 and 1962 (known as the Drug Efficacy Study Implementation program), an 8-way study was performed, and the FDA concluded that dicyclomine hydrochloride did not contribute to the effectiveness of the other two ingredients. Therefore, the product was reformulated in 1976 and dicyclomine hydrochloride, for which no benefits were observed, was removed from the formulation. The medicine began to be manufactured as a dual combination product (doxylamine succinate and pyridoxine hydrochloride).

There is a considerable amount of published information available on the pregnancy outcomes of Debendox in humans, including at least 11 separate studies from several different hospitals and university groups across America, Europe and Australia with the triple combination product of doxylamine/pyridoxine/dicyclomine, involving overall thousands of women, then several later studies with the dual combination product doxylamine/pyridoxine. These studies, as they became available, were considered by regulators all over the world in consideration of the medicine's safety.

We cannot be certain when use of the triple combination product will have stopped but this is anticipated to be by the early 1980s. In studies looking at patients who took Debendox at any point after 1976 or into the early eighties, these may have included either or both of the dual and triple combination formulation.

Please see below a list of publications of studies, relevant to the triple combination product, which included data on the overall risk of birth defects. This list is separated into 3 groups according to how certain we can be about whether they concern the triple combination product. Please note that the drug Debendox had

other trade names in different geographical regions, hence the trade names Bendectin or Lenotan may be referred to.

In Group 1 there are 12 publications where, from the drug exposure date in the study (up to 1976) and/or by explicit statement in the publication, exposure to the triple combination product can be ascertained. Two reports (Shapiro 1977 and Heinonen 1980) were taken from the same data source (the USA collaborative Perinatal Project) so we have conservatively referred to that as one, hence a total of 11.

In Group 2, there is one further study (Erickson 1991) which spanned the window 1968-1980. We don't know from the report whether patients in this study were mostly taking the triple combination or the dual combination product. However, the study window comprised at least 8 years (1968-1976) where Bendectin would have been the triple combination product.

Group 3 includes two further studies from during the period 1977 – 1979 (Jick 1981 and Morelock 1982) where it is possible some of the mothers exposed to Bendectin received the triple combination product, though the dual combination product was already being manufactured in this period.

There is one further study in Group 3 concerning the period 1969 – 1974 (Greenberg 1977) where, in a summary table, doxylamine is referred to, however it is uncertain if (but likely) this comprised exposure to doxylamine in the triple combination product.

A summary of this collection of studies is shown in the tables below. From the information provided in the literature articles, it can be ascertained that one study was funded by Merrell Dow (Bunde 1963) and one study was part funded by the USA Food and Drug Administration (FDA), the National Institute of Neurological and Communicative Disorders and Stroke, and a grant from Merrell laboratories (Shapiro 1977).

The other literature articles cite independent sponsorship or studies have been run by government bodies and health agencies.

Group 1: STUDIES INCLUDING DATA FROM EXPOSURE TO THE TRIPLE COMBINATION PRODUCT OF DOXYLAMINE/PYRIDOXINE/DICYCLOMINE

Report Main Author, Year	Time Population studied	Place of Population studied	Main authors Affiliation	Funding Information available from paper	Conflict of interests identified from paper
Bunde 1963	Prior to 1963	USA: (California, Colorado,	Merrell Inc	Paper from Department of Medical Research,	Paper from Departme

		Illinois, Ohio, Pennsylvania) Canada (Ontario, Quebec)		The Wm. S, Merrell Co, Division of Richard-Merrell Inc	nt of Medical Research, The Wm. S, Merrell Co, Division of Richard-Merrell Inc
GPRU 1963	Prior to 1963	Great Britain	Great Britain General Practitioner Research Group (150 members)	-	-
Milkovich 1976	Pre 1975	USA: (San Francisco, California)	Child Health and Development Studies, School of Public Health, University of California, Berkeley, California	Grant No HD 07256 of the National Institute of Child Health and Human Development of the National Institutes of Health	-
Shapiro 1977	Up to 1976 analysis dicyclomine and doxylamine which included Bendectin	USA, the Collaborative Perinatal Project - 12 hospitals throughout the United States- Boston, New Orleans, Philadelphia, Virginia, New York, Minnesota, Oregon, Tennessee	Drug Epidemiology Unit, Boston University Medical Center and the Harvard School of Public Health.	Supported by Contract 223-75-3036 from the Food and Drug Administration, Contract NO1-NS-2-2322 from the National Institute of Neurological and Communicative Disorders and Stroke, and by-grants from Hoffmann-La Roche Inc., Nutley, New Jersey, and Merrell National Laboratories, Cincinnati, Ohio.	Part Funded by a grant from Merrell

Newman 1977	1953 - 1975	Australia, (Tasmania)	The University of Tasmania, Hobart Tasmania.	-	-
Smithells 1978	1974-1975	England (Leeds and Liverpool)	Department of Paediatrics and Child Health, University of Leeds, England	-	-
Michaelis 1980	1964-1972 Interim report 1980, (later report 1983)	West Germany, 21 hospitals	Insitut für Medizinische Statistik und Dokumentation der Universität 6500 Mainz, Bundesrepublik, Deutschland	Deutsche Forschungsgemeinschaft DFG, German Research Foundation	-
Heinonen 1980	1959-1974	USA, Collaborative Perinatal Project starting			Legal testimony: David Mekdeci v. Merrell National Laboratories; US District Court, Middle District of Florida.
Fleming 1981	Mid 1960s	Scotland and England	Birmingham Research Unit of the Royal College of General Practitioners,	-	-

			Birmingham; Scottish General Practitioner Research Unit, University of Dundee, Dundee		
Gibson 1981	1975-1979 (triple formulation stated)	Australia, Adelaide	The Queen Victoria Research Foundation, Adelaide; Department of Human Nutrition, Commonwealth Scientific and Industrial Research Organisation Australia (Government Agency)	-	-
Eskenazi 1982	1974-1976	USA Connecticut	John B. Pierce Foundation Laboratory and the Departments of Epidemiology and Public Health and Obstetrics and Gynecology, Yale University School of Medicine.	Supported in part by United States Public Health Service Grant No. 5-T32-ES 7086 (to Dr. Eskenazi) from the National Institute of Environmental Sciences and by Contract No. NOI-HD-5-2800 and Grant No. HD-I 1357 (to Dr. Blacken) from the National Institute of Child Health and Human Development.	-

Shiono 1989	1974-1977 1959 to 1966	USA (13 clinics in California) Kaiser Permanente Birth defects study (triple combination product) Collaborative Perinatal Project, 12 university centres - doxylamine data capture	National Institutes of Health, National Institute of Child Health and Human Development, Prevention Research Program, Bethesda, Maryland	The Kaiser Permanente Birth Defects Study was supported by contract number NOI-HD-2861 from the Center for Population Research, NICHD.	-

Group 2: STUDY HIGHLY LIKELY TO INCLUDE DATA FROM EXPOSURE TO THE TRIPLE COMBINATION PRODUCT OF DOXYLAMINE/PYRIDOXINE/DICYCLOMINE

Report Main Author, Year	Time Population studied	Place of population studied	Main authors Affiliation	Funding Information available from paper	Conflict of interests identified from paper
Erickson 1991	1968-1980 Temporal distribution of Bendectin exposure not detailed. Study window comprised at least 8 years where Bendectin would have	USA Atlanta	Birth Defects and Genetic Diseases Branch, Centers for Disease Control, Atlanta, Georgia	Centers for Disease Control	

	been the triple combination.				

Group 3: STUDIES WHERE IT IS UNCERTAIN BUT COULD INCLUDE DATA FROM EXPOSURE TO THE TRIPLE COMBINATION PRODUCT OF DOXYLAMINE/PYRIDOXINE/DICYCLOMINE

Report Main Author, Year	Time Population studied	Place of population studied	Main authors Affiliation	Funding Information available from paper	Conflict of interests identified from paper
Greenberg 1977	1969 -1974 (in summary table stated as doxylamine- may be some uncertainty whether this is exclusively doxylamine alone or whether this included doxylamine in combination)	Great Britain	Medicines Division, Department of Health and Social Security, London. Medical Statistics Division, Office of Population Censuses and Surveys, London	-	-
Jick 1981	1977-1979	USA Seattle	Boston Collaborative Drug Surveillance Program, Boston University Medical Center; Group Health Cooperalive	Supported in part by grant FD 01009 from the Food and Drug Administration and by grants from the Wyman-	-

			of Puget Sound, Seattle; The Embryology Teratology Unit, Children's Service, Massachusetts General Hospital, Boston.	Gordon Foundation, Worcester, Mass, and the New England Peabody Home for Crippled Children, Boston, and by grant No. HD 15241 from the National Institutes of Health.	
Morelock 1982	1977 -1979	USA Boston	Boston University School of Medicine and School of Public Health and the Departments of Pediatrics and Socio-Medical Sciences and Community Medicine, Boston City Hospital	Supported by National Institute on Alcohol Abuse and Alcoholism Grant Nos. ROJ-AA02446, R01-AA01257, and R01-AA0213J-04.	-

The studies we refer to in the groups above are published in scientific articles available from various international journals. MHRA does not itself hold these articles, therefore under copyright law, we do not have the right to provide you with copies of the articles. However, please see below a list of the citations. You can request the articles through the British Library or your local public library.

We trust that this information is useful and provides an answer to your questions.

Citations of articles discussed.

Bunde, C.A., and Bowles D.M. (1963) A technique for controlled survey of case records. ***Current. Therapeutic Research,* 5 : 245-248.**

General Practitioner Research Group (1963) General practitioner clinical trials: Drugs in pregnancy survey. ***The Practitioner, 191: 775- 780.***

Milkovich, L., and van den Berg, B. J. (1976) An evaluation of the teratogenicity of certain antinauseant drugs. ***American Journal of Obstetrics & Gynecology, 125: 244 -248.***

Shapiro, S., Heinonen, O.P., Siskind, V., Kaufman, D.W., Monson, R.R., and Slone D. (1977) Antenatal exposure to doxylamine succinate and dicyclomine hydrochloride (Bendectin) in relation to congenital malformations, perinatal mortality rate, birth weight and intelligence quotient score. ***American Journal of Obstetrics & Gynecology, 128: 480-485.***

Newman, N.M., Correy, J.F. and Dudgeon G.I. (1977) A survey of congenital abnormalities and drugs in a private practice. ***Australia and New Zealand Journal of Obstetrics and Gynaecology, 17: 156-159.***

Smithells, R.W., and Sheppard, S. (1978) Teratogenicity testing in humans: A method demonstrating safety of Bendectin. ***Teratology, 17: 31-35.***

Michaelis, J., Gluck, E., Michaelis, H., Koller, S., and Degenhardt, K.H. (1980) Does Lenotan have teratogenic effects? ***Deutsches Ärzteblatt., 23: 1527-1529***

Michaelis, J. Michaelis, H., Glück, E., and Koller, S. (1983) Prospective Study of Suspected Associations Between Certain Drugs Administered During Early Pregnancy and Congenital Malformations. ***Teratology 27: 57-64***

Heinonen, O.P. (1980) Legal testimony: David Mekdeci v. Merrell National Laboratories; ***United States District Court, Middle District of Florida, 1980. Transcripts of Proceedings: 4143-4152***.

Fleming, D.M., Knox, J.D.E. and Crombie D.L. (1981) Debendox in early pregnancy and fetal malformation. ***British Medical Journal, 283: 99-101.***

Gibson, G.T., Colley, D.P., McMichael, A.J. and Hartshorne J.M. (1981) Congenital anomalies in relation to the use of doxylamine/dicyclomine and other antenatal factors. ***Medical Journal of Australia, 1: 410-414***.

Eskenazi, B., and Bracken M.B. (1982) Bendectin (Debendox) as a risk factor for pyloric stenosis. ***American Journal of Obstetrics & Gynecology, 144: 919-924.***

Shiono, P.H., and Klebanoff, M.A. (1989) Bendectin and human congenital malformations. ***Teratology, 40: 151-155.***

Erickson, J.D. (1991) Risk factors for birth defects: Data from the Atlanta Birth Defects Case-Control Study. ***Teratology, 43: 41-51.***

Greenberg, G., Inman, W.H.W., Weatherall., J.A.C., Adelstein, A.M. and Haskey J.C. (1977) Maternal drug histories and congenital abnormalities. ***British Medical Journal*, 2: 853-856.**

Jick, H., Holmes, L.B., Hunter, J.R., Madsen, S. and Stergachis, A. (1981) First trimester drug use and congenital disorders. ***Journal of the American Medical Association, 246: 343-346.***

Morelock, S., Hingson, R., Kayne, H., Dooling, E., Zuckerman, B., Day, N. Alpert, J.J. and Flowerdew, G. (1982) Bendectin and fetal development. ***American Journal of Obstetrics & Gynecology, 142: 209-213.***

The MHRA continuously monitors the safety of vaccines through a variety of pharmacovigilance processes, including the Yellow Card scheme. As part of our signal detection processes, all adverse reaction reports received by the Yellow Card scheme are assessed, and cumulative information is reviewed at regular intervals. If appropriate, regulatory action would be taken if any serious risks were confirmed.

I hope the information provided is helpful, but if you are dissatisfied with the handling of your request, you have the right to ask for an internal review. Internal review requests should be submitted within two months of the date of this response; and can be addressed to this email address.

Yours sincerely,

FOI Team,
Vigilance and Risk Management of Medicines Division

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