

TABLE OF CONTENTS

Page

1.	BENEFITS OF ACCUTANE	1
1.1	Etiology and Pathology of Acne.....	1
1.2	Acne Treatments.....	2
1.2.1	Topical therapies.....	2
1.2.2	Antibiotics.....	3
1.2.3	Accutane Therapy.....	4
2.	ACCUTANE USE AND ACNE PHARMACOEPIDEMIOLOGY	5
2.1	Overview.....	5
2.2	Estimating Accutane Use.....	6
2.3	Accutane Use and Acne Prevalence	10
2.3.1	Estimating Acne Epidemiology	10
2.3.2	NHANES Point Prevalence Of Acne.....	11
2.3.2.1	Prevalence Estimates in Adolescents.....	12
2.3.2.2	Prevalence Estimates in Adults.....	13
2.3.2.3	Duration Estimates.....	13
2.3.2.4	Summary of Prevalence Estimates	14
2.4	Accutane Use	15
2.5	Acne Treatment Visits	16
2.5.1	Survey of Physicians for Medical Management	18
2.6	Accutane Use and Reports of Pregnancy.....	23
2.6.1	Introduction.....	23
2.6.2	Issues Regarding Spontaneous Reporting of Pregnancies	25
2.6.3	Pregnancy Incidence in Accutane-Treated Women in the Accutane Survey Conducted by the Slone Epidemiology Unit	26
2.6.4	Representativeness of the Accutane Survey Population to All Women Prescribed Accutane	29
2.6.5	Retrospective Study of Pregnancy Incidence in Accutane-Treated Females and Matched Controls in the UnitedHealthcare Database	30
2.6.5.1	Study Methodology.....	31
2.6.5.2	Results	31
2.6.5.3	Discussion.....	32
2.6.6	Pregnancy Rate in Clinical Trial Using Accutane (isotretinoin)	32
2.7	Summary.....	32
3.	PREGNANCY PREVENTION PROGRAM: A RISK MANAGEMENT PROGRAM TO REDUCE PREGNANCIES DURING ACCUTANE TREATMENT	33
3.1	Development of the Roche Pregnancy Prevention Program.....	33
3.1.1	Before Adoption of the Roche Pregnancy Prevention Program	33
3.1.1.1	Category X and Strong Warnings Against Use During Pregnancy	33
3.1.1.2	Labeling Changes and Dear Doctor Letters.....	33
3.1.1.3	Educational Programs.....	34
3.1.2	Adoption of the Roche Pregnancy Prevention Program	34
3.1.2.1	Unprecedented, Strong Warnings	34
3.1.2.2	Female Patient Informed Consent.....	34
3.1.2.3	Warnings on Package.....	35

3.1.2.4	Pregnancy Prevention Programsm for Women on Accutane® (isotretinoin) [PPP Kit].....	35
3.1.2.5	Accutane Survey.....	35
3.1.2.6	Accutane Prescriber Tracking Survey.....	36
3.1.2.7	Annual and Quarterly Meetings With FDA.....	36
3.1.2.8	Educational Efforts.....	36
3.2	Assessment of Impact of Pregnancy Prevention Program on Patient and Prescriber Behaviors.....	36
3.2.1	Assessable Changes in Physician and Patient Behaviors.....	36
3.2.2	Accutane Prescriber Tracking Survey.....	37
3.2.2.1	Accutane Survey.....	38
3.3	Pregnancies.....	38
3.3.1	Analysis of Data Relating to Pregnancies.....	38
3.3.1.1	Patient Education and Pregnancy.....	39
3.3.1.2	Pregnancies that occurred at the beginning of Accutane therapy.....	39
3.3.1.3	Pregnancies that occurred during therapy.....	39
3.3.1.4	Consistent Patterns in the Manner in Which Women Continue to Become Pregnant During Accutane Therapy.....	40
3.3.1.5	No Consistent Pattern of Patient Characteristics or Demographics for Pregnancies.....	40
3.3.1.6	No Consistent Pattern of Prescriber Specialty or Characteristics for Pregnancies.....	41
3.3.2	Conclusions.....	41
3.4	Targeted Pregnancy Prevention Program.....	42
3.4.1	Summary of Data Reviewed.....	42
3.4.2	Development of Targeted Pregnancy Prevention Program.....	42
3.4.3	Parts of the Targeted Pregnancy Prevention Program (T-PPP).....	42
3.4.3.1	Part One: Excluding Pregnancy before Therapy Is Initiated.....	43
3.4.3.2	Part Two: Preventing Pregnancies That Occur During Therapy.....	44
3.4.4	Part Three – Measures for Data Collection - Process Goals.....	50
3.4.4.1	Changes in the Accutane Survey.....	51
3.4.4.2	Prescriber and patient information.....	52
3.4.4.3	Behavioral Research.....	53
3.4.5	Part Three – Measures for Data Collection and Metrics for Assessing Overall Success of All Parts – Objective Goals.....	53
3.4.5.1	Annual Review with the Agency of Process Goals and Analysis of Assessment Data.....	53
3.5	Summary.....	54
4.	HORMONAL CONTRACEPTIVE EVALUATION PROGRAM.....	55
4.1	Background.....	55
4.2	In Vitro Inhibition and Induction Studies.....	55
4.3	Clinical Studies.....	56
4.3.1	Hormonal Contraceptive Physiology.....	56
4.3.2	Ortho Novum 7/7/7.....	56
4.3.3	Primary Objectives of the Clinical Studies.....	57
4.3.4	Patient Selection Criteria and Study Enrollment.....	57
4.3.5	Study Design.....	57
4.3.6	Interim Results from Clinical Study NR15888.....	57
4.3.6.1	Study Population.....	58
4.3.6.2	Interim Pharmacodynamic Results.....	58
4.3.6.3	Safety Results.....	58
4.3.7	Results from Clinical Study NR15792.....	58
4.3.7.1	Study Population.....	58
4.3.7.2	Pharmacodynamic Results.....	59

4.3.7.3	Safety Results	59
4.4	Overall Conclusions.....	59
5.	PSYCHIATRIC CONDITIONS	60
5.1	Overview.....	60
5.2	Risk Assessment Program	60
5.3	Adolescence, Acne, and Psychiatric Conditions.....	61
5.3.1	Adolescence as a Risk Factor	61
5.3.2	Alcohol and Substance Abuse as Cofactors	63
5.3.3	Acne as Contributor to Psychological Distress.....	63
5.4	Natural History of Psychiatric Disease.....	65
5.4.1	Terminology	65
5.4.2	Depression and Other Mood Disorders	65
5.4.2.1	Presentation.....	65
5.4.2.2	Depression	65
5.4.3	Symptomatology of Psychotic Disorders	66
5.4.4	Suicidal Ideation and Suicidal Behavior.....	67
5.5	Pharmacoepidemiological Analysis of Spontaneous Reports.....	70
5.5.1	Objectives	70
5.5.2	Methodological Overview	71
5.5.3	Principal Findings and Conclusions	72
5.5.3.1	Depression and Other Mood Disorders	72
5.5.3.2	Psychotic Disorders	72
5.5.3.3	Suicidal Behavior.....	73
5.6	Complementary Analyses	73
5.6.1	Analysis in a Prospective Clinical Trial, NR15645	73
5.6.1.1	Study Design.....	74
5.6.1.2	Beck Depression Inventory.....	74
5.6.2	Retrospective Analysis of Epidemiological Databases.....	74
5.6.2.1	Objectives	74
5.6.2.2	Definition of Cohorts	75
5.6.2.3	Results	75
5.7	Review of Literature on Retinoids and the Central Nervous System	76
5.7.1	Overview.....	76
5.7.2	Retinoid receptors in the brain.....	76
5.7.3	Prenatal and postnatal exposure to retinoids.....	77
5.7.4	Summary.....	78
5.8	Overall Conclusions on Psychiatric Conditions	78
6.	REFERENCES.....	78

LIST OF TABLES

Table 1	Estimated New Patient Prescriptions for Accutane (Females and Males)*.....	9
Table 2	Prevalence of Different Components of Acne by Age in Australian School Children*	12
Table 3	Age and gender comparison of estimated point prevalence of severe acne and moderate acne with active cysts (NHANES) to Accutane utilization in 1998.16	
Table 4	Number of Visits Per Year (X 1000) and Percent of Visits for Acne, as Primary Reason/Diagnosis (1995-1997)*	17

Table 5	Percent of Total New Acne Patients By Age Group	21
Table 6	Survey of Prescribing Behavior.....	22
Table 7	Number of Reported Pregnancies (U.S. Data Only) Since 1982.....	24
Table 8	Analysis of Adverse Events and Pregnancies Associated with Accutane Therapy.....	25
Table 9	Pregnancy Rate from Accutane Survey According to the Year of Enrollment and Accutane Course*.....	27
Table 10	Pregnancy Rates* by Age Group by Enrollment Year#.....	28
Table 11	Comparison of Percent of SEU Enrollees to total enrollment by age category to percent of female patients receiving prescriptions (NDC)	30
Table 12	Frequency and Incidence Rate# of Pregnancy ϕ Among Female Accutane Users (N=2,532) and Non-Users (N=12,636).....	31
Table 13	The Accutane Prescriber Tracking Survey Results	38
Table 14	New 10-Step Program	48
Table 15	Submission Dates for the In Vitro Drug Interaction Studies	56
Table 16	Significant Treatment-Related Changes in Psychologic Factor Scores: Before-Treatment versus After-Treatment Comparisons (from Rubinow et al., 1987).....	64
Table 17	DSM-IV Criteria for Major Depressive Disorder (adapted).....	66
Table 18	Prevalence Rates* of Major Depressive Disorders for 15-24 Year Olds (Males and Females)	66
Table 19	Prevalence Rates* of Psychotic Disorders for 15-24 Year Olds (Males and Females).....	67
Table 20	Observed vs. Predicted Suicides for 15-24 Year Olds in an Accutane-Exposed Cohort (U.S. Data and Estimates).....	73

LIST OF FIGURES

Figure 1	Estimated Number of Patients Using Accutane.....	8
Figure 2	Mean Number of Office Visits for Typical Acne Patients in a 12-Month Period	20
Figure 3	Suicide: A Multi-Factorial Event (adapted from Jacobs DG, 1997)	69
Figure 4	Suicide Rate (Per 100,00 Persons) for All Persons and Persons Aged 15 to 24 Years from 1900-1990 (U.S. Data).....	70