

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-830

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
NDA 20-829/20-830¹
SINGULAIR™
(MONTELUKAST SODIUM)

Division of Pulmonary Drug Products
(HFD-570)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

¹NDA 20-829 are film coated tablets, 10 mg. NDA 20-830 are chewable tablets, 5 mg.

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-829/20-830²

SINGULAIR™

(MONTELUKAST SODIUM)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for SINGULAIR™, Merck Research Laboratories/Merck and Co., Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Montelukast Sodium is a chemically synthesized drug which is administered as Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg for the prophylaxis and chronic treatment of asthma, including the prevention of day- and night time symptoms, the treatment of aspirin-sensitive patients, and the prevention of exercise-induced bronchoconstriction. The drug substance is manufactured by Merck Manufacturing Division in Ireland³. The drug product manufacture and packaging occurs in North Carolina. The intermediate red color concentrate used in formulation

²NDA 20-829 are film coated tablets, 10 mg. NDA 20-830 are chewable tablets, 5 mg.

³NOTE: In a separate communication to the Agency, the applicant confirmed that the certification of compliance from Merck, Ireland which had been annotated as confidential could be included with the non-confidential EA.

is manufactured by Merck Manufacturing Division in Pennsylvania. The finished drug product will be used throughout the United States.

Montelukast Sodium may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. Therefore, the applicant has submitted a tier 0 EA without format items 7, 8, 9, 10 and 11 in accordance with the *Guidance for Industry for the Assessment in Human Drug Applications and Supplements*.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned drug product will be disposed of at a permitted incinerator on-site or at an alternate permitted off-site facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4.30.97
DATE
Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

5/14/97
DATE
Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

HFD-570/B. Kuzmik original to NDA 20-829 & 20-830
HFD-357/FONSI File 20829/20830
HFD-357/Docket File
HFD-205/FOI COPY

**APPEARS THIS WAY
ON ORIGINAL**

1. Date

January 1, 1997

2. Name of Applicant

Merck Research Laboratories

Merck and Co., Inc.

3. Address

Sumneytown Pike

West Point, PA. 19486

4. Description of the Proposed Action

a. Requested Action

Merck & Co., Inc. is filing a New Drug Application requesting the approval of SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg). Drug substance manufacture will take place at the Merck Manufacturing Division facility located in Ballydine, Ireland. Drug product manufacture and packaging will take place in Wilson, North Carolina. A red color concentrate intermediate, used in the drug product formulation of SINGULAIR™ (Montelukast Sodium Chewable Tablets, 5 mg), is manufactured at the Merck Manufacturing Division facility located in West Point, Pennsylvania for use at the Wilson, North Carolina facility.

b. Need For Action -

SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg) is indicated in adult and pediatric patients 6 years of age and older for the prophylaxis and chronic treatment of asthma, including the prevention of day- and nighttime symptoms, the treatment of aspirin-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction. The dosage for adults 15 years of age and older is one 10-mg tablet daily to be taken at bedtime. The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily to be taken at bedtime. Because of the therapeutic benefits associated with its availability and use, approval is justified and preferable to non-approval.

The packaging components selected for marketing SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg) consist of high density polyethylene (HDPE) bottles (30 mL, 75 mL, 14 oz, and 96 oz) with either child resistant or non child resistant screw caps and aluminum induction seals or cold formed all aluminum peelable blisters.

The total annual quantity to be manufactured anticipated over a five year period post-approval to support the U. S. market for SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg) is given in Confidential Appendix IV - Part 1.

c. Locations Where the Product will be Produced and the Types of Environments
Adjacent to Those Locations

The synthesis of bulk active montelukast sodium will occur at the Merck Manufacturing Division facility located in Ballydine, Ireland. The drug product will be formulated and packaged at the Merck Manufacturing Division facility located in Wilson, North Carolina. A red color concentrate intermediate, used in the drug product formulation of SINGULAIR™ (Montelukast Sodium Chewable Tablets, 5 mg), will be manufactured at the Merck Manufacturing Division facility located in West Point, Pennsylvania for use at the Wilson, North Carolina facility.

The certification of compliance from the Merck Manufacturing Division facility located in Ballydine, Ireland is included in Confidential Appendix III. The type of environment present at the Wilson, North Carolina facility is described below.

Returned U.S. marketed product will be disposed of by the Merck Manufacturing Division facility located at West Point, PA. The type of environment at West Point, Pennsylvania facility is described in Section 4.e..

1) Wilson, North Carolina

Merck & Co., Inc.
I-95 and Highway 264
4633 Merck Road
Wilson, North Carolina

a) Geographic Conditions

Wilson is located 45 miles east of Raleigh, North Carolina.

The plant is located 4.5 miles west of Wilson on a 225-acre plot, near the intersection of Interstate Highway 95 and Highway US 264, at latitude 35° 45' N longitude 78° 00' W.

Land use surrounding the plant is primarily residential and agricultural.

b) Air Resources

Air quality in the region meets the National Ambient Air Quality Standards (NAAQS) for sulfur oxides, nitrogen oxides, total suspended particulates and ozone. The annual rainfall is approximately 42 inches, and the average annual temperature is 59°F. Prevailing winds are from the southwest at an average annual speed of 7.7 mph.

c) Water Resources

Potable water is obtained from the local public water supply for the City of Wilson. The City of Wilson supplies the water to the site. The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices. Wastewater from the facility is routed to the City of Wilson treatment facility. In the developed area of the property, there are six natural

c) Water Resources (Cont.)

drainage tributaries exiting the plant property and one entering the property. There is an established stormwater monitoring point for monitoring all stormwater releases from the plant site.

d) Land Resources

The plant site consists mainly of gently sloping terrain with forest and open farmland underlain by the Coastal Plain Providence to the east and the Piedmont Geologic Providence to the west. The coastal plain soils are marine deposits and the piedmont soils are residual, formed from the chemical decomposition of the underlying bedrock. Both soils are interbedded sands, silts, and clays with the typical depth to bedrock 20 to 40 feet. The plant site elevation is about 160 feet above mean sea level.

d. Locations where the Product will be Used and the Types of Environments Present at and Adjacent to those Locations

The product is intended for use throughout the United States.

e. Locations where the Product will be Disposed of and the Types of
Environments Present at and Adjacent to those Locations

Merck & Co., Inc. has a domestic return goods policy which involves the return of any unused market packages to the West Point, Pennsylvania location for evaluation and disposal. The product is disposed of at the West Point facility by incineration or an approved off-site facility, and any ash generated is land filled at a permitted off-site facility. This essentially results in a single location for control of product disposal. The types of environments present at the disposal plant site are described below.

1) West Point, Pennsylvania

Merck Manufacturing Division
Summeytown Pike
West Point, Pennsylvania

a) Geographic Conditions

The West Point plant is located on a site (~450 acres) in Upper Gwynedd Township, Montgomery County, which is approximately 30 miles northwest of Philadelphia. The center of the West Point plant is located near latitude 40° 12' 54" N and longitude 75° 17' 59" W. Land use surrounding the plant is primarily residential and agricultural with other industrial sites approximately one-half mile away.

b) Air Resources

Air quality in this area is in compliance with the Environmental Protection Agency's (EPA) National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for total suspended particulates, sulfur oxides, and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Protection (PA DEP) under the requirements of the State Implementation Plan. At this time, Montgomery County does not meet the ozone standard set forth by the NAAQS.

The West Point plant lies within the outer zone of the Southeast Pennsylvania air basin. Pennsylvania is part of the EPA Region III and PA DEP is responsible for implementing the State Implementation Plan which includes new stationary source permits for manufacturing. Meteorological data for the region is collected at the Philadelphia International Airport. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient monthly temperature varies between 33 and 77°F (0.5-25°C). Predominant winds are from west to southeast.

c) Water Resources

Potable water is supplied to the plant operations via an on-site storage tank which is supplied by on-site wells and a public water supplier, North Wales Water Authority. The plant potable water quality meets all requirements of the Federal and State Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Stormwater is managed using detention basins which control site runoff and regulate discharge to the Towamencin Creek or the Wissahickon Creek.

Wastewaters generated as a result of the incineration of returned goods is collected, equalized, and discharged to the Upper Gwynedd Township Sewer Department. The Upper Gwynedd Township Sewer Department discharges treated effluent to the Wissahickon Creek.

The location of the discharge from the Upper Gwynedd Township Sewer Department is downstream from the West Point site. Pennsylvania DEP limits the wasteload allocation and water pollutant limits (established by the Pennsylvania Water Toxics Management Act) from the Upper Gwynedd Township Sewer Department by means of the National

c) Water Resources (Cont.)

Pollutant Discharge Elimination System discharge permit. This wasteload allocation and water pollutant limit are used to determine the allowable contribution limits from the West Point site. The treated wastewater is also regulated by the Upper Gwynedd Township Sewer Department under permit and local ordinance.

d) Land Resources

The plant is underlain by Triassic age sedimentary rocks, mapped as the Brunswick and Lockatong formations. These formations occur as layered beds of red and very dark gray shale with occasional layers of sandstone. Although these rocks generally have low primary porosity, permeability is maintained and improved by the presence of fractures and joint sets.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

Information concerning the chemical structure, empirical formula, molecular weight, chemical names, generic name, trade name and CAS (Chemical Abstracts Service Registry) number can be found in Appendix I.

6. Introduction of Substances Into the Environment

a. Substances expected to be emitted and estimated releases

1) Bulk drug synthesis

Confidential Appendix III contains the certification of compliance with appropriate environmental regulations and permits for the Merck Manufacturing Division facility located in Ballydine, Ireland. Because the site is in compliance with the appropriate environmental regulations and permits with respect to manufacture of bulk drug, no adverse environmental impacts are anticipated.

2) Dosage Form Production

Confidential Appendix IV - Part 2 summarizes the chemical substances which may be expected to enter the various environmental compartments (atmospheric, aquatic, terrestrial) as a result of the drug product manufacture and packaging at the Merck Wilson, North Carolina facility and as a result of formulation of the red color concentrate intermediate at the Merck West Point, Pennsylvania facility. Packaging activities will not contribute emissions to the air, water, or land which would adversely impact the environment.

3) Use Sites

Administered dosage form will normally enter the environment in highly diluted aqueous domestic sewage which will be subject to further local treatment. The maximum expected emitted concentration (MEEC) resulting from the use of montelukast sodium has been estimated based on the projected maximum annual production level anticipated over a five year period post-approval needed to supply the U.S. market (see Expected Introduction Concentration - Use in Confidential Appendix IV - Part 1). This estimate assumes excretion of 100% of the drug activity and no environmental depletion. Use of the drug is not expected to result in emissions to the atmospheric or terrestrial environmental compartments.

4) Disposal Site

The Merck West Point, Pennsylvania incineration facilities will be used to treat return product. On-site incineration facilities will handle the majority of this waste with resulting combustion efficiency of at least 99.9% on an hourly basis. In the event that the West Point facility is unable to accept such waste, the wastes will be disposed of at an alternate permitted off-site facility. Expected emissions are described in the following sections.

4) Disposal Site (Cont.)

- (1) Air Emissions - Typical combustion products are expected to be emitted into the atmosphere from the incineration of returned goods. The on-site West Point facility incineration operation is in compliance with all applicable standards and permit limits. Any off-site incineration will be conducted at an equivalent, permitted facility.
- (2) Liquid Emissions - Any wastewater generated from the incinerator operation will be discharged into the sanitary sewer which undergoes on-site equalization and is discharged for off-site biological wastewater treatment at the Upper Gwynedd Township Sewer Department.
- (3) Solid Emissions - All returned and outdated market packages and residual waste from operations at the West Point, Pennsylvania facility will be incinerated at on-site or off-site facilities permitted to handle such waste streams.

b. Control Procedures and Citations of Compliance

1) Wilson, North Carolina

a) Air Emissions Controls and Citations - Drug Product Formulation and Packaging

The dust produced by the manufacturing operation that may be emitted into the atmosphere will be controlled by dust collectors. Specific ventilation systems for packaging consisting of filtration and collection provide for particulate removal. The particulate emissions are controlled to meet the requirements of the site permit, No. 4884R11 (expiration date: 3/31/97), ~~as amended, issued by~~ the State of North Carolina Department of Natural Resources.

The operation of the Wilson manufacturing, packaging and power generating facilities is allowed and in compliance with Air Permit Number 4884R11, as amended, issued by the North Carolina Department of Natural Resources and Community Development in accordance with Article 21B, Chapter 143, General Statutes of North Carolina and "Other Laws, Rules and Regulations".

Approval of the proposed action will not impact the facility's ability to comply with all applicable air emission requirements. Air emissions from drug product formulation

a) Air Emissions Controls and Citations - Drug Product Formulation and Packaging (Cont.)

may include the substances listed in Confidential Appendix IV - Part 2.

b) Liquid Emissions Controls and Citations - Drug Product Formulation and Packaging

In order to minimize liquid emissions as a result of drug product formulation, the equipment used to formulate montelukast sodium will be cleaned by vacuuming to remove residual dust on the equipment. Prior to discharge to the City of Wilson collection system for processing in the Public Works Treatment Facility, the site measures the flow and periodically samples the effluent to verify compliance with the permit requirements. The facility is subject to the permit limits established by Sewer Discharge Permit Number 8406 (expiration date: 6/30/2001). The results from 10 years of operation indicate the multiproduct pharmaceutical facility's source control measures have satisfactorily met the discharge levels set forth in the permit.

The discharge of wastewater to the City of Wilson Wastewater Collection system is allowed under the site

b) Liquid Emissions Controls and Citations - Drug Product Formulation and Packaging (Cont.)

- Sewer Connection and Discharge Permit Number 8406. The site discharge is limited to daily maximum discharges of: 88,000 gallons per day, pH between 5.0-11.0, chlorides up to 200 mg/L, oil/grease up to 200 mg/L, cadmium up to 0.0249 lbs/d, cyanide up to 0.0221 lbs/d, lead up to 0.1094 lbs/d and zinc up to 0.6469 lbs/d. These permit limits are established under the city's "Rules and Regulations for the Discharge of Wastewaters into the Wastewater Treatment System of the City of Wilson, North Carolina". The City of Wilson Department of Public Works Wastewater Treatment Plant operates under National Pollutant Discharge Elimination System (NPDES) Permit Number NC0023906. No new permit limits are anticipated as a result of the proposed action.

Approval of the proposed action will not impact the facility's ability to comply with the conditions of the wastewater agreement. Chemical substances that may be discharged into the wastewater are listed in Confidential Appendix IV - Part 2.

c) Solid Waste Controls and Citations - Drug Product Formulation and Packaging

Any solid waste resulting from drug product formulation and packaging that contains pharmaceutical residuals will be collected for disposal and sent to an off-site incineration or landfill facility, permitted by Federal, State and local agencies. No hazardous solid waste will be generated by the formulation or packaging processes.

The Wilson plant is in compliance with the North Carolina Solid Waste and Hazardous Waste Management Rules. These requirements assure comprehensive control for the management of waste throughout the plant including returned market packages that are sent to West Point for disposal. These regulations are subject to the requirements of the Federal Resource Conservation and Recovery Act (RCRA) and the Federal Hazardous and Solid Waste Amendments (HSWA). These regulations do not limit the quantity of solid waste generated. However, recycling will be implemented to the fullest extent possible to minimize the amount of solid waste generated. No new permit limits are anticipated as a result of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

Control Documentation

I. Summary

F. Environmental Assessment

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals required by the Occupational Safety & Health Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety & Health Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix II for a copy of the MSDS for the drug substance.

2) West Point, Pennsylvania

a) Air Emission Controls and Citations - Red Color Concentrate Intermediate Formulation and Drug Product Disposal

Air emissions from formulation of the red color concentrate intermediate will include the substances identified in Confidential Appendix IV - Part 2. Dust produced by the formulation that may be emitted to the atmosphere will be controlled by product filters and/or dust collectors with greater than 90% control efficiency. Emissions will be controlled to less than 0.04 grains/dscf, as required by the regulations.

a) Air Emission Controls and Citations - Red Color Concentrate
Intermediate Formulation and Drug Product Disposal (Cont.)

The on-site incineration facility employs necessary operating conditions to ensure compliance with permitted emission levels in Permits 400459 (expiration: 6/16/2005) and 46-301-191C (expiration: 6/19/99) issued by PA DEP and Permit PAD002387926 (expiration: 3/19/2006) issued by both EPA and PA DEP. As a contingency, off-site incineration will be conducted at a permitted facility.

The air emission controls for the disposal of this product meet the requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Article III - Department of Environmental Protection (PA DEP), Chapters 121-141.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

Control Documentation

I. Summary

F. Environmental Assessment

b) Liquid Waste Controls and Citations - Red Color Concentrate Intermediate Formulation and Drug Product Disposal

The liquid emissions from the manufacturing operations and from the incineration operation for returned goods will be discharged into the site wastewater collection system and will undergo equalization along with other sanitary waste. Liquid emissions resulting from the formulation of the red color concentrate intermediate will include constituents identified in Confidential Appendix IV - Part 2. In general, manufacturing equipment will be cleaned by vacuuming to remove residual dust thereby minimizing the discharge of substances to the wastewater treatment facility.

The effluent from the West Point site is treated by the Upper Gwynedd Township Sewer Department, and this effluent is discharged from the Upper Gwynedd Township Sewer Department under NPDES Permit Number PA 0023256. This permit is administered by PA DEP.

The wastewater is subject to and in compliance with the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439. The wastewater is also regulated by the Upper Gwynedd Township Sewer

b) Liquid Waste Controls and Citations - Red Color Concentrate
Intermediate Formulation and Drug Product Disposal (Cont.)

Department and is in compliance with the existing contract and the "Rules and Regulations Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of Upper Gwynedd Township Sewer Department". These regulations are based on the requirements of the Federal Clean Water Act and Pennsylvania Clean Streams Law. The current contract with Upper Gwynedd Township Sewer Department (expiration: 3/23/2013) limits plant effluent to a flow (calculated from a monthly average) of 1.225 million gal/day; BOD = 250 mg/L (daily maximum); TSS = 150 mg/L (monthly average); and pH between 5.5 - 9.0.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Red Color Concentrate
Intermediate Formulation and Drug Product Disposal

Any solid waste resulting from formulation of the red color concentrate intermediate will either be incinerated on-site or sent off-site to a disposal facility, permitted by Federal, State and local agencies. No hazardous solid waste will be generated by the process.

c) Solid Waste Controls and Citations - Red Color Concentrate Intermediate Formulation and Drug Product Disposal (Cont.)

Appropriate controls for the disposal of unused market packages are utilized as part of the site solid waste management program. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with prevailing solid waste regulations. Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 400674 and 400459 (expiration: 1/25/2003 and 6/16/2005, respectively) issued by PA DEP and Permit PAD002387926 (expiration date: 3/19/2006) issued by both EPA and PA DEP. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part I - Department of Environmental Protection, Chapter 75, are the primary regulations which impact solid waste management. The regulations are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act.

c) Solid Waste Controls and Citations - Red Color Concentrate
Intermediate Formulation and Drug Product Disposal (Cont.)

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. The facility is not currently limited by the amount of wastes generated, although efforts will be made to minimize the amount of solid wastes generated.

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals required by the Occupational Safety & Health Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety & Health Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix II for a copy of the MSDS for the drug substance.

c. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the formulation and packaging of SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg) at the Wilson, North Carolina facility and the formulation of a red color concentrate intermediate and the disposal of returned goods at its facility in West Point, Pennsylvania; as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the formulation and packaging of SINGULAIR™ (Montelukast Sodium Film Coated Tablets, 10 mg and Chewable Tablets, 5 mg) at the Wilson, North Carolina facility and the formulation of a red color concentrate intermediate and disposal of returned goods at its facility in West Point, Pennsylvania.

7. Fate of Emitted Substances to the Environment

The expected environmental concentration resulting from use and/or disposal is expected to be less than one (1) ppb (see Confidential Appendix IV - Part 1). Based on this expected environmental concentration, the Guidance document (CDER, 1995) indicates that information for this section is not required and, consequently, is not being provided.

8. Environmental Effects of Released Substances

The expected environmental concentration resulting from use and/or disposal is expected to be less than one (1) ppb (see Confidential Appendix IV - Part 1). Based on this expected environmental concentration, the Guidance document (CDER, 1995) indicates that information for this section is not required and, consequently, is not being provided.

9. Use of Resources and Energy

The expected environmental concentration resulting from use and/or disposal is expected to be less than one (1) ppb (see Confidential Appendix IV - Part 1). Based on this expected environmental concentration, the Guidance document (CDER, 1995) indicates that information for this section is not required and, consequently, is not being provided.

10. Mitigation Measures

The expected environmental concentration resulting from use and/or disposal is expected to be less than one (1) ppb (see Confidential Appendix IV - Part 1). Based on this expected environmental concentration, the Guidance document (CDER, 1995) indicates that information for this section is not required and, consequently, is not being provided.

11. Alternatives to the Proposed Action

The expected environmental concentration resulting from use and/or disposal is expected to be less than one (1) ppb (see Confidential Appendix IV - Part 1). Based on this expected environmental concentration, the Guidance document (CDER, 1995) indicates that information for this section is not required and, consequently, is not being provided.

12. List of Preparers

Stuart Bacher

B.S. - Chemical Engineering, 1961

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M.S. - Chemical Engineering, 1964

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Laura M. Tyls

B.S. - Chemical Engineering, 1987

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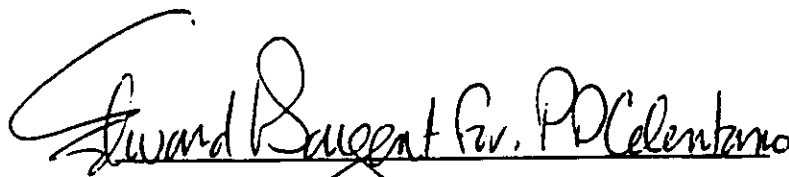
Manhattan College, Riverdale, NY

Senior Project Engineer, Toxicology & Environmental Health

Merck Manufacturing Division

13. Certification

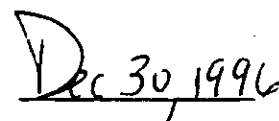
The undersigned certify that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for the preparation of the environmental assessment.



Mr. Perry D. Celentano

Vice President, Safety & the Environment

Merck & Co., Inc.



Date

14. Literature Cited

Center for Drug Evaluation and Research (CDER),
"Guidance for Industry for the Submission of an
Environmental Assessment in Human Drug Applications and
Supplements," November 1995.

APPENDICES

APPENDIX I - DRUG SUBSTANCE INFORMATION SUMMARY

APPENDIX II - MATERIAL SAFETY DATA SHEET (MSDS) FOR DRUG
SUBSTANCE

APPENDIX III - ^{NON}CONFIDENTIAL - CERTIFICATION OF COMPLIANCE FROM
^{FDA Supplement}MERCK FOREIGN MANUFACTURER

APPENDIX IV - CONFIDENTIAL - CHEMICALS SUBJECT TO THE PROPOSED
ACTION EXPECTED INTRODUCTION CONCENTRATION

APPENDIX I
DRUG SUBSTANCE INFORMATION SUMMARY

APPENDIX I

A. Drug Substance Information Summary

1. Nomenclature

a. Names

Chemical Names:

[R-(E)-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-
3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]
cyclopropaneacetic acid, sodium salt

Generic Name (USAN):

Montelukast sodium

Trademark:

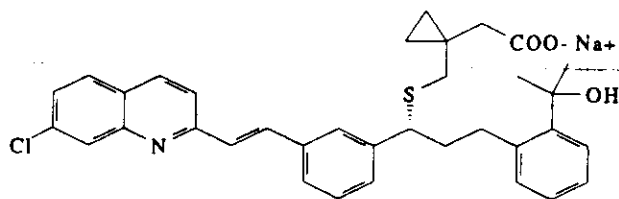
SINGULAIR® (Montelukast Sodium Tablets and Chewable
Tablets)

CAS Registry Number:

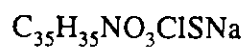
151767-02-1

b. Formulas and Molecular Weight

Structural Formula



Molecular Formula:



Molecular Weight:

608.2