

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-829

ADMINISTRATIVE DOCUMENTS

APPENDIX II

MATERIAL SAFETY DATA SHEET (MSDS) FOR DRUG SUBSTANCE

Montelukast Sodium
Chemical and Pharmaceutical Manufacturing and
Control Documentation

I. Summary
F. Environmental Assessment

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: MONTELUKAST SODIUM
PLANT MSDS CODE: BA-062

PAGE: 1 OF 8
Date: 11/96

1. Chemical Product and Company Identification

Manufacturer----- MERCK SHARP AND DOHME (IRL) LTD.
BALLYDINE, KILSHEELAN,
CLONMEL, COUNTY TIPPERARY,
IRELAND

Emergency Telephone Number----- 051-601000 (Ireland)
1-908-594-5555 (U.S.)

Label Name----- Montelukast Sodium

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

Synonyms----- (R)-1-[[[1-(3-(2-(7-Chloro-2-quinolinyl)
ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)
phenyl]propyl]thiomethyl]cyclopropane
acetic acid sodium salt;
MK-0476, L-706,631; Singulair(TM)

Material Statistical Number----- 2-02440

Material Product Number----- Not available

Intended Use----- Anti-asthmatic; Leukotriene D4 (LTD4)
Antagonist.

2. Composition/Information on Ingredients

<u>Component</u>	<u>Molecular Formula</u>	<u>Molecular Weight</u>	<u>CAS Number</u>	<u>Percent (%)</u>
Montelukast Sodium	C ₃₅ H ₃₅ ClNO ₃ Na	608.2	151767-02-1	100%
EC Label-----			Xi, R41	

3. Hazards Identification

Appearance----- Clean white to off white powder.

Emergency Overview----- **WARNING!**
Pharmaceutical active ingredient.
Anti-asthmatic drug.
Risk of serious damage to eyes.
Mildly irritating to skin.

*** Continued on next page ***

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Potential Health Effects-----

Practically non-toxic by ingestion. Mildly
irritating to the skin. Severely
irritating to the eyes.

4. First-Aid Measures

Eye Contact-----

In case of contact, immediately flush eyes
with plenty of water for at least 15
minutes. Get medical attention
immediately.

Skin Contact-----

In case of contact, immediately flush skin
with plenty of water while removing
contaminated clothing and shoes. Get
medical attention if symptoms occur. Wash
clothing before reuse. Thoroughly clean
shoes before reuse.

Inhalation-----

Get medical attention immediately. If
inhaled, remove to fresh air. If not
breathing, give artificial respiration. If
breathing is difficult, give oxygen.

Ingestion-----

Get medical attention if symptoms appear.
Do NOT induce vomiting unless directed to
do so by medical personnel. Never give
anything by mouth to an unconscious person.

Note to Physicians-----

Not available

5. Fire-Fighting Measures

Flash Point (°C/°F)-----

Not applicable

Flash Point Test Method-----

Not applicable

Flammable Limits-LEL (%)-----

Not applicable

-UEL (%)-----

Not applicable

Autoignition Temperature (°C/°F)-

Not available

Oxidizing Properties-----

Not available

Combustibility Information-----

Not available

*** Continued on next page ***

I. Summary
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PRODUCT NAME: MONTFELUKAST SODIUM
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Dust Explosivity Information----

Tests show a minimum ignition energy between 10 and 30 milliJoules. At this energy level all plant and equipment should be grounded. The hazard from electrostatic discharges from dust clouds should be considered.

Shock Sensitivity-----

Not available

Fire/Explosion Hazards-----

Not available

Extinguishing Media-----

In case of fire, use water spray (fog), foam, dry chemical or CO₂.

Special Fire Fighting Procedures-

Fire fighters should don SCBA and protective clothing.

Hazardous Decomposition Products Resulting From a Fire-----

CO, CO₂, phosgene and oxides of nitrogen and sulphur may be released in a fire.

6. Accidental Release Measures

Personal Precautions-----

Immediately contact emergency personnel. Keep unnecessary personnel away. Use suitable protective equipment (Section 8). Follow all fire fighting procedures (Section 5).

Environmental Precautions-----

Avoid contact of spilled materials and runoff with soil and surface waterways.

Methods for Cleaning Up-----

If emergency personnel are unavailable, vacuum or carefully scoop up spilled materials and place in an appropriate container for disposal. Avoid creating dusty conditions.

For additional assistance in the U.S., CHEMTREC provides a toll-free

Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.

7. Handling and Storage

Handling-----

Avoid contact with skin and eyes. Do not ingest. Refrain from smoking or eating when handling. Wash thoroughly after use. Prevent product dust generation. If exposure is likely wear protective equipment (See Section 8).

*** Continued on next page ***

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PRODUCT NAME: MONTELUKAST SODIUM
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Storage-----
Store in a closed container in a cool, dry, well-ventilated location. Keep container closed when not in use. Protect from exposure to light and moisture.

Other-----
Avoid electrostatic charging of product by the following grounding measures: ground containers during filling and emptying; ground all conductive installation parts of filling equipment; avoid non-conductive layers on conductive supports.

8. Exposure Controls/Personal Protection

Exposure Guidelines

Component	Irish Occupational Exposure Limit (OEL)	OSHA Permissible Exposure Limit (PEL)	ACGIH Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Montelukast Sodium	Not established	Not established	Not established	0.1 mg/m3 (8hr-TWA)

Engineering Controls

Ventilation-----
No special containment is required. Local exhaust ventilation should be provided.

Personal Protective Equipment

Eye/Face Protection-----
Safety glasses are required. Goggles, face shield or other full-face protection is required if potential exists for direct exposure to dust or aerosols.

Hand/Arm Protection-----
Latex gloves, or gloves providing greater protection, are required. Double latex gloves are recommended.

Respiratory Protection-----
An approved, properly fit tested, HEPA filtered cartridge respirator, or a respirator of greater protection, is required.

Additional Protective Equipment-----
Laboratory coat or work uniform is required. Disposable outer garments are required if there is the potential for contact with dust. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets).

*** Continued on next page ***

I. Summary

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9. Physical and Chemical Properties

Appearance-----	Clean white to off white powder
Odour/Threshold Level (ppm)-----	No odour
pH-----	9.4-10.2
Boiling Point/Range (°C/°F)-----	Not applicable
Melting Point/Range (°C/°F)-----	275.9°F (135.5°C)
Solubility in water-----	Greater than 100 mg/ml at approximately 25°C
Partition Coefficient (Kow)-----	The partition coefficient, expressed as Log P, is 2.3.
Specific Gravity (Water=1)-----	(bulk density)
Vapour Density (Air=1)-----	Not applicable
Vapour Pressure (mmHG @ °C/°F)---	Not applicable
Volatile Components (% w/w)----- Q	None

10. Stability and Reactivity

Stability-----	Photolabile, hygroscopic
Conditions to Avoid-----	Exposure to light or moisture
Incompatibilities-----	Not available
Hazardous Polymerizations-----	Will not occur
Hazardous Decomposition Products-	

11. Toxicological Information

<u>Primary Route(s) of Entry</u> -----	Inhalation: Yes
	Ingestion: No
	Skin Contact: No

*** Continued on next page ***

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Toxicity Data

<u>TEST</u>	<u>SPECIES</u>	<u>ROUTE</u>	<u>RESULT</u>
Acute	Rat	Oral	LD50 Greater than 5000 mg/kg
Acute	Mouse	Oral	LD50 Greater than 5000 mg/kg
Irritation	Rabbit	Dermal	Mildly irritating
Irritation	Rabbit	Ocular	Severely irritating

Effects of Acute Exposure

Eye Contact----- Severely irritating to the eyes.

Skin Contact----- Mildly irritating to the skin.

Inhalation----- No data available

Ingestion----- Practically non-toxic by ingestion. In clinical trials, MK-0476 has been well tolerated, producing only mild adverse reactions. Adverse reactions considered possibly drug-related included headache, facial flushes, diarrhea, abdominal discomfort, sleepiness, light-headedness, eye twitching, nasal congestion and transient elevations in liver enzymes and bilirubin. The anticipated clinical dose is expected to range between 10 and 50 mg/day.

Effects of Chronic Exposure-----

Montelukast sodium is a drug being developed for the treatment of asthma. In subacute and chronic studies minimal toxicity has been observed. Findings have been confined primarily to the slight, but transient increases in liver enzymes in rats only, and gastrointestinal tract distension by gas production attributable to the detergent effect of the compound. Occasional post-dosing salivation has also been noted. In reproductive and developmental toxicity studies in rats and rabbits, evidence of fetotoxicity and decreased fertility and fecundity were only observed at dosages toxic to adult animals. MK-0476 was negative in a battery of genotoxicity assays.

Carcinogen Designation-----

Not listed as a carcinogen by OSHA, IARC, or NTP.

Medical Conditions Aggravated by Exposure-- Not available

*** Continued on next page ***

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12. Ecological Information

Environmental Fate-----

The partition coefficient, expressed as Log P, is 2.3. The compound degrades very rapidly in aqueous media under natural light.

Environmental Effects-----

The compound is considered to be moderately toxic.

LC50 Daphnia Magna, 48 hrs.
LC50 Fathead minnow, 96 hrs.
LC50 Rainbow trout
EC10 ASRIT
EC50 Microtox(TM)

Greater than 1.5 mg/l
Greater than 1.5 mg/l
4.47 mg/l
Greater than 1.5 mg/l
Greater than 1.5 mg/l

13. Disposal Considerations

Waste Disposal Information-----

Dispose of or treat all spill residues including contaminated soils following all applicable regulations.

14. Transport Information

Shipping Description

U.S. DOT-----
IATA/ICAO-----
IMO-----
ADR-RID-----

Not Regulated, Drugs or Medicines, NOI
Not Regulated, Drugs or Medicines, NOI
Not Regulated, Drugs or Medicines, NOI
Not available

15. Regulatory Information

U.S. Federal Regulations-----

Not available

International Regulations-----

Not available

State Regulations-----

This material Safety Data Sheet is written in compliance with the following Irish Legislation: The Safety, Health and Welfare at Work Act 1989 and The European Communities (Classification, Packaging, Labelling and Notification of Dangerous Substances) Regulations, 1994.

*** Continued on next page ***

Montelukast Sodium
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16. Other Information

Date Prepared-----	June 1996
Last Revision Date-----	November 1996
MSDS Co-ordinator-----	1-908-423-7926 Merck & CO, Inc. One Merck Drive P.O. Box 100, WS2F-48 Whitehouse Station, NJ 08889-0100 USA

Disclaimer: While this information and recommendations set forth
are believed to be accurate as of the date hereof,
MERCK & CO, INC. makes no warranty with respect hereto
and disclaims all liability from reliance thereon.

Division of Pulmonary Drug Products

PROJECT MANAGER REVIEW

NDA: 20-829 and 20-830

Names of Drugs:

SINGULAIR (montelukast sodium) Tablets, 10mg (NDA 20-829)

SINGULAIR (montelukast sodium) Chewable Tablets, 5mg (NDA 20-830)

Sponsor: Merck Research Laboratories

Material Reviewed

Submission Date: February 21, 1997

Receipt Date: February 21, 1997

Review

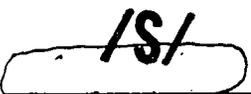
1. In the cover letter for NDA 20-830, the check # and User Fee I.D. # are identical to the check # and User Fee I.D. # for NDA 20-829. The company, when questioned about it, acknowledged that this is an error. Two separate checks were written with different numbers, one for each application. Although the User Fee I.D.# for NDA 20-830 is incorrect in the cover letter, it is marked correctly on the User Fee Cover Sheet.
2. The cover letter indicates that Items 1, 2, 3, and 4 are specific for each application and therefore, NDA 20-829 may contain different information from NDA 20-830. Items 5 through 13, however, are identical for each application. The sponsor explains that asthma is similar in adults and children, certainly in individuals ages 6 years and older. Therefore, data on the use of montelukast sodium in adults and in children are each pertinent to and supportive of the other. The defined items are referred to in the left hand column of the Index to Contents of Application.
3. In the cover letters of each NDA, the sponsor includes the statement that they did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.
4. FDA form 356h is completed correctly for both NDAs. A microbiology section is not included (not required).
5. FDA form 3397 (User Fee Cover Sheet) is completed correctly for both applications.
6. Patent information

U.S. Patent #5,565,473 (expiration date November 30, 2010)

7. A Quality Assurance statement is included that states that data presented in these applications were subject to audit based on approved standard operating procedures in effect at the time of the audit.
8. Both NDAs are formatted as required in 21 CFR 314.50. Volume 1.1 contains the overall Index to Contents of the Application by volume number and page number. It also includes a summary of the regulatory background information for the applications. The Synopsis of Application, which is the overall summary, is included in Vol. 1.2. For Items 6, 8, and 10, the references begin with page number 1000. It should also be noted that Items 11 and 12 (Case Report Tabulations and Case Report Forms) for these applications are being provided in electronic format only. A formal waiver from the requirements of 21 CFR 314.50(f) was granted to the sponsor by Dr. Janet Woodcock (FDA) on January 29, 1997. The hard copies of these items contain only the Table of Content and Introduction.

Conclusions

1. The applications are fileable from an administrative perspective.


Betty Kuzmik
Project Manager

cc:
NDA 20-829
NDA 20-830
Division Files
HFD-570/Kuzmik
HFD-570/Schumaker


3/12/97

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

14 pages

NDA 20-829 SINGULAIR™
(Montelukast Sodium Film Coated Tablet)
Patent Information

Item 13

**PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES**

- | | | |
|----|---|--|
| 1. | Active Ingredient: | Montelukast sodium |
| 2. | Dosage: | 10 mg |
| 3. | Trade Name: | SINGULAIR™ |
| 4. | Dosage Forms: | Film Coated Tablet |
| | Route of Administration: | Oral |
| 5. | Applicant Firm Name: | Merck Research Laboratories |
| 6. | NDA Number: | 20-829 |
| 7. | Approval Date: | Pending |
| 8. | Exclusivity - Date First ANDA
Could be Submitted | Five years from the approval date of
NDA 20-829 |
| | Length of Exclusivity | To be determined |
| 9. | Applicable Patent Numbers | 5,565,473
Expiration Date: November 30, 2010 |

EXCLUSIVITY SUMMARY for NDA # 20-829 _____ SUPPL # N/A _____

Trade Name Singulair Tablets Generic Name montelukast sodium

Applicant Name Merck Research Laboratories

HFD- 570

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES / X / NO / ___ /

b) Is it an effectiveness supplement?
YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__5 years from date of approval__

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # YES /__/	!	NO /__/ Explain: _____
	!	_____
Investigation #2	!	
IND # YES /__/	!	NO /__/ Explain: _____
	!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /__/ Explain _____	!	NO /__/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /__/ Explain _____	!	NO /__/ Explain _____
_____	!	_____
_____	!	_____

Montelukast Sodium
Chemical and Pharmaceutical Manufacturing and
Control Documentation

I. Summary

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APPENDIX III

~~CONFIDENTIAL~~

FDA non-confidential per applicants

CERTIFICATION OF COMPLIANCE FROM MERCK
FOREIGN MANUFACTURER

Chemical and Pharmaceutical Manufacturing and
Control Documentation

I. Summary

F. Environmental Assessment

Merck Sharp & Dohme (Ireland)
Ballydine, Kilsheelan,
Clonmel,
Co. Tipperary,
Ireland.
Telephone (051) 640411
Fax (051) 640836



18 October 1996

Merck Sharp & Dohme (Ireland) states that it is in compliance with all local and national environmental laws, or on an enforceable schedule to be in compliance with all emission requirements set forth in all permits applicable to the production of Montelukast Sodium at its facility in Ballydine, Ireland and that any subsequent increase in production at the facility is not expected to affect compliance with the current emission requirements or compliance with environmental law.



D. J. Buckley
Senior Director of Operations
Ballydine Plant, Merck Manufacturing Division.

18 Oct 1996

18 October 1996.

DIRECTORS: E.J. Clee (U.K.) J.C.R. Collis (U.K.) M.A. Hacker (U.S.A.) B.J. Kelley (U.S.A.)
J.C. Lowent (U.S.A.) D.F. Maaria (U.S.A.) A.J. Kearney (U.S.A.) D. Theret (France)
Incorporated in Bermuda. Registered in Dublin No. E2980.

MEMORANDUM

TO: NDA 20-829/20-830 (montelukast sodium)

FROM: Peter Honig, MD
Medical Team Leader
Division of Pulmonary Drug Products (HFD-570)

RE: Proprietary Name for Montelukast

DATE: May 19, 1997

PH 5/19/97

This memo is written in response to the Merck submission in which the sponsor requests that DPDP revisit the acceptability of the trademark name Singulair. The sponsor acknowledges that there does not appear to be a "sound-alike" problem with other currently marketed drugs. This is always the major concern for the Agency and is not a factor in this case. The major objections of the LNC focused around potential future changes in the dosing regimen which would make the name Singulair an unreliable proprietary name for dosing recommendations and the potential for the name to allow the sponsor to promote the drug as the only drug needed for asthma.

The sponsor responds by indicating that, for scientific as well as marketing reasons, the once-daily dosing regimen will not be modified. Due to its pharmacokinetic and receptor binding characteristics, it is highly unlikely that the drug will be used more often than once daily. Furthermore, for marketing purposes, a once-daily regimen is optimal for the company.

The sponsor responds to the potential promotional misuse of the name Singulair by indicating that Merck has an internal medical-legal review process that will ensure appropriate use of the trademark. The sponsor also states that the trademark review and promotional review are separate issues, and the trademark should not be rejected based upon speculation involving future, yet to be prepared, promotional material.

Reviewer recommendation: This response has been evaluated by the montelukast review team and, after consideration of the sponsor's response, there was no objection to the trademark Singulair. This has been discussed with Drs. Jenkins and Bilstad who concur.

MEMORANDUM

DATE: February 9, 1998

TO: NDA 20-829, NDA 20-830 **ISI** 2/19/98

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-829, for Singulair (montelukast sodium) Tablets, and NDA 20-830, for Singulair (montelukast sodium) Chewable Tablets, were originally submitted by Merck Research Laboratories on February 21, 1997. NDA 20-829 seeks an indication in adolescents and adults and NDA 20-830 seeks an indication in children and young adolescents. The current user fee goal date for NDA 20-829 and NDA 20-830 is February 21, 1998.

Clinical

NDA 20-829:

The sponsor proposes that Singulair Tablets be indicated for chronic, maintenance treatment of asthma in patients 15 years of age and older. In support of this indication, the sponsor submitted several large, randomized, double-blind, placebo-controlled trials in patients with asthma, including patients not previously maintained on inhaled corticosteroids (ICS) and patients previously maintained on ICS. Please refer to the medical officer review prepared by Dr. Honig for a more detailed review of the studies submitted by the sponsor. Selected important trials which support the proposed indication and which are reflected in the draft labeling will be briefly discussed in this memorandum. Note that in the pivotal trials Singulair was dosed at 10-mg once-daily in the evening. The sponsor submitted the results of several Phase 2 dose-ranging studies, which supported a conclusion that doses above 10-mg once-daily did not provide any additional clinical benefit.

Study 31 and Study 20 were similarly designed 12-week clinical trials in patients with mild to moderate persistent asthma at baseline. The major difference in the two trials was the inclusion of a low-dose beclomethasone (400 mcg/day ex-valve from a non-US formulation which delivered 100 mcg/puff ex-valve, a spacer device was also used) active control arm in Study 20. In both studies the primary endpoints were FEV₁ assessed at each clinic visit and daytime asthma symptom scores recorded by patients in a diary. Numerous other secondary endpoints were also specified in the protocol. In Study 31, the mean percent change in FEV₁ averaged over the 12-week treatment period was 4.22% and 13.05% for placebo and montelukast, respectively. During the three-week, single-blind washout period, patients who remained on montelukast continued to demonstrate improvement in FEV₁, while patients

randomized from montelukast to placebo demonstrated a fall in mean FEV₁ toward the placebo values. In this trial, montelukast was also significantly better than placebo for daytime asthma symptom scores, rescue beta-agonist use, morning PEF, and nocturnal asthma symptom score. In Study 20, the mean percent change in FEV₁ averaged over the 12-week treatment period was 1.07%, 7.49%, and 13.30% for placebo, montelukast, and beclomethasone, respectively. While montelukast was significantly more effective than placebo for FEV₁, daytime asthma symptom score, and most of the secondary endpoints, beclomethasone was consistently significantly more effective than montelukast on these same endpoints.

Study 31 and Study 20 clearly demonstrate that montelukast is more effective than placebo in patients with mild to moderate asthma; however, Study 20 strongly suggests that low-dose beclomethasone is more effective than montelukast for these patients groups.

Study 15 was a 4-week, randomized, double-blind, placebo-controlled trial in asthmatic patients with a documented history of aspirin sensitivity. The design of this trial and the pre-specified endpoints were very similar to those employed for Study 31 and Study 20. The mean percent change in FEV₁ averaged over the 4-week treatment period was -1.74% and 8.55% for placebo and montelukast, respectively. Montelukast was also significantly more effective than placebo for daytime asthma symptom scores and most other secondary endpoints. While this trial supports the effectiveness of montelukast in asthmatics with a documented history of aspirin sensitivity, cross-study comparisons of the treatment effect size for montelukast versus placebo indicate that montelukast is not uniquely more effective in this group than in the broader population of asthmatics. Importantly, this trial did not assess the response to aspirin in patients treated with montelukast.

Study 42 was a 12-week, randomized, placebo-controlled trial in patients with asthma and a documented clinically significant fall in FEV₁ in response to exercise. Exercise challenges were performed at baseline and periodically throughout the course of the 12-week trial to assess the impact of chronic montelukast therapy on the response to exercise. The exercise challenges were performed near the end of the dosing interval (i.e., at 20-24 hours after the preceding dose). Exercise challenges were not performed at any other time in the dosing interval. Over the course of the 12-week trial, montelukast was significantly more effective than placebo in decreasing the mean FEV₁ AUC_{0-60 min}, mean maximum percent fall in FEV₁, and time to recovery to within 5% of pre-exercise baseline FEV₁. While these results suggest that chronic therapy with montelukast blunts the response to exercise in patients with documented exercise induced bronchospasm, careful analysis of the mean maximum percent fall in FEV₁ and a post-hoc categorical analysis of this endpoint call into question the clinical significance of these findings. The mean maximum percent fall in FEV₁ for the montelukast group at baseline was 38.3% and decreased to 22.26%, 20.33%, and 20.91% at weeks 4, 8, and 12, respectively. Thus, the mean maximum percent fall in FEV₁ remained above 20% (the traditional cutoff for defining a positive response to exercise), indicating that a significant number of the patients treated with montelukast continued to have a clinically significant decline in FEV₁ in response to exercise. A post-hoc, categorical analysis of the maximum percent fall in FEV₁ for individual patients revealed that 52% of montelukast patients had

>20% fall in FEV₁ while on therapy (versus 72% of placebo patients). Based on these results, and similar results for shorter-term crossover trials, I believe that montelukast should not be approved for a specific indication of exercise induced bronchospasm. Further, I believe that the categorical analysis of FEV₁ described above should be included in the labeling and that the labeling should clearly state that patients with EIB who are on montelukast therapy should continue to use their usual regimen of prophylactic beta-agonist prior to exercise (unless otherwise directed by their physician) and should continue to have a short-acting beta-agonist available for rescue use during exercise.

Study 46 employed a complex study design in which patients who were receiving various doses and formulations of ICS were enrolled into a lead-in period during which their ICS dose was tapered by protocol toward their lowest effective dose. The patients were then randomized to a 12-week, double-blind, placebo-controlled period. During the double-blind period, the patient's ICS doses were titrated based on protocol defined criteria with the primary endpoint being the last tolerated ICS dose as a percent change from baseline. It is worthwhile to note that patients entered this study on a wide variety of ICS formulations (both MDIs and DPIs), many of which are not available in the US. The study is also somewhat flawed by the fact that there was an implicit assumption that the nominal doses of ICS were equi-effective. These design flaws serve to limit the interpretation of the results of this trial to a qualitative rather than a quantitative level. Over the course of the double-blind period, the montelukast group demonstrated a 46.73% decrease in ICS requirement from baseline versus a decline of 30.27% for the placebo group. In perhaps a more clinically meaningful analysis, 40.2% of montelukast patients were able to be titrated completely off ICS and remained off ICS at the end of the 12 week treatment period versus 29.2% for placebo. This study supports a conclusion that addition of montelukast to patients already receiving ICS for treatment of asthma may allow the ICS dose to be tapered without significant loss of asthma control. It is not clear; however, whether the results of this study can be generalized to all patients receiving ICS or to patients receiving oral corticosteroids.

Study 29 also employed a complex study design to assess whether the combination of montelukast and beclomethasone provided added clinical benefit over beclomethasone or montelukast alone in patients previously maintained on low-dose ICS (beclomethasone 336 mcg/day). The results of this study demonstrated that the combination of montelukast and beclomethasone was significantly better than beclomethasone alone or placebo for FEV₁ averaged over the last ten weeks of the 16-week double-blind treatment period. Also notable from this study was the observation that beclomethasone alone was more effective than montelukast alone. This finding serves to validate the observations from the beclomethasone versus montelukast comparison noted above from study 20; i.e., the NDA contains two studies which demonstrate that low-dose beclomethasone is clinically superior to montelukast. This finding provides important data for clinicians as they determine where montelukast should fit into the treatment regimen for individual patients and, therefore, should be included in the labeling.

(Note: The sponsor had previously been informed by the Division that the active comparison

arm of Study 20 would not support any comparative claims for promotion or labeling since the beclomethasone active control arm in that study was a non-US formulation. This decision was based on the fact that the comparison would have little meaning to US prescribers since the comparator formulation was not available in the US and it was impossible to state how the beclomethasone formulation used in Study 20 compared to available US formulations. I now believe that it is appropriate to represent the active control arm of Study 20 in the US labeling for montelukast for two primary reasons; 1) the findings in Study 29, in which a US formulation of beclomethasone was used, provide confirmation of the findings of Study 20, and 2) it is important that these comparative findings be available to US clinicians as they incorporate montelukast into their treatment armamentarium for asthma.)

The safety profile of montelukast in patients 15 years of age and older was generally benign with adverse events occurring at a rate greater than for placebo primarily limited to non-serious gastrointestinal signs and symptoms. There was also a signal that montelukast may result in elevation of hepatic transaminases in a small percentage of patients. No cases of severe elevations or drug-induced hepatitis occurred in the NDA database and it appeared that the frequency of hepatic transaminase elevations decreased with time suggesting that any liver toxicity is not related to cumulative dose. There was no evidence in the NDA database for the type of eosinophilic vasculitis syndromes, including Churg Strauss Syndrome, which have been reported for zafirlukast, another leukotriene receptor antagonist. While this provides some comfort, it should be noted that the majority of cases reported in patients receiving zafirlukast have occurred in patients who were being tapered from oral corticosteroids; a patient group that was not studied in the montelukast NDA database.

NDA 20-830:

The sponsor proposes that Singulair Chewable Tablets be indicated for the chronic, maintenance treatment of asthma in patients 6 to 14 years of age. Please refer to the medical officer review prepared by Dr. Trontell and the Medical Team Leader Memorandum prepared by Dr. Honig for more complete details of the clinical program conducted by the sponsor in patients 6-14 years of age. The sponsor chose the proposed 5 mg once-daily dose for the chewable tablets in children based on pharmacokinetic comparisons to the plasma concentrations of montelukast demonstrated to be safe and effective in adults in clinical trials using a 10-mg once-daily dose. The sponsor then conducted Study 49, an 8-week, double-blind, randomized, placebo-controlled trial in patients with mild to moderate asthma 6-14 years of age to validate the efficacy and safety of the 5-mg once-daily dose. The results of Study 49 demonstrated that the mean change from baseline in FEV₁ averaged over the 8-week treatment period was 4.16% and 8.71% for placebo and montelukast, respectively ($p < 0.001$). Montelukast was also numerically more effective than placebo on secondary endpoints such as rescue beta-agonist requirements, morning PEF, daytime asthma symptom scores, and nocturnal asthma symptom scores.

A second clinical trial, Study 40, evaluated the efficacy of the 5-mg once-daily dose in patients 6-14 years of age with a documented history of exercise induced bronchospasm. In this

crossover study, montelukast was significantly more effective than placebo in decreasing the response to exercise as measured by FEV₁, AUC_{0-60 min} and by the mean maximum percent fall in FEV₁ post exercise. While the clinical significance of these findings are suspect for the same reasons described above for the adult EIB studies, these findings do support that the 5 mg once-daily dose is effective through the end of the dosing interval since the exercise challenges were performed at or near the end of the dosing interval (i.e., 20-24 hours after the preceding dose).

Post-hoc cross-study comparisons of the treatment effect size observed for montelukast in pediatric patients suggest that the effect size of the 5-mg dose may be smaller than that seen with the 10-mg dose in adults. This observation, combined with the fact that no dose-ranging trials were done in pediatric patients, raises the question of whether the 5 mg once-daily dose is the optimal dose for pediatric patients. While the 5-mg once-daily dose has been shown to be more effective than placebo, the sponsor should be urged to conduct

The safety profile of montelukast pediatric patients was generally similar to that observed in adults.

There are no outstanding clinical issues and both NDAs are approvable from a clinical perspective once a few remaining issues related to representations of the clinical trial data in the package insert are agreed between the division and the sponsor.

Pre-clinical

The sponsor conducted an extensive battery of in vitro and animal studies designed to evaluate the pharmacologic and toxicologic profile of montelukast. Please refer to the pharmacology/toxicology review prepared by Dr. Williams and the Team Leader Memorandum prepared by Dr. Sun for more complete details of the results of these studies. Montelukast was not teratogenic in rats or rabbits, although impairment of fertility was observed in female rats. These findings support a Pregnancy Category B statement in the labeling. Montelukast was not genotoxic in a battery of in vitro and in vivo assays and was not carcinogenic in lifetime studies conducted in rats and mice.

There are no outstanding issues and both NDAs are approvable from a preclinical perspective with acceptable labeling.

CMC

Singulair Tablets are film coated and contain 10.4-mg montelukast sodium, equivalent to 10

mg of the free acid. Singulair Chewable Tablets contain 5.2-mg montelukast sodium, equivalent to 5 mg of the free acid. Please refer to the reviews prepared by Dr. Leak for a more detailed description of the CMC sections of the NDAs.

There are no outstanding issues and both NDAs are approvable from a CMC perspective with acceptable labeling.

Clinical Pharmacology and Biopharmaceutics

Montelukast is a selective cysteinyl leukotriene receptor antagonist. The sponsor submitted PK information for both the 10-mg film-coated tablet and the 5-mg chewable tablet. For a more detailed discussion of the clinical pharmacology and biopharmaceutics data submitted to these NDAs please refer to the review prepared by Dr. Chen. Summary PK parameters for the 10 mg tablet include a T_{max} of 3-4 hours, mean oral bioavailability of 64%, linear pharmacokinetics up to a dose of 50 mg, and a mean plasma half-life of 2.7-5.5 hours. Summary PK parameters for the 5-mg chewable tablet include a T_{max} of 2-2.5 hours, mean oral bioavailability of 73% in the fasted state, and mean oral bioavailability of 63% in the fed state. Montelukast is extensively metabolized by the liver by cytochrome P450 3A4 and 2C9 and the primary route of elimination of the parent compound and its metabolites is in the bile. The sponsor submitted data to show that the pharmacokinetic profile of the 5 mg chewable tablet in children 6-14 years of age was similar to that observed for the 10-mg tablet in adolescents and adults 15 years of age and older. As noted above, this pharmacokinetic comparison was the basis for the sponsor's dose selection for the 5-mg tablet in children 6-14 years of age; no dose ranging trials were conducted. The sponsor conducted a battery of drug interaction studies and found no significant effect of montelukast on the PK of warfarin, theophylline, digoxin, terfenadine, fexofenadine, oral contraceptives, prednisone, or Phenobarbital, a hepatic enzyme inducer, caused a 40% decrease in montelukast AUC.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable with appropriate labeling.

Data Verification

The Division of Scientific Investigations performed audits of four clinical sites involved in the pivotal clinical trials for these NDAs (3 sites for NDA 20-829, 1 site for NDA 20-830). Two of the three sites audited for NDA 20-829 received an NAI rating by the DSI reviewer, the third site received a VAI rating. The minor discrepancies noted at the VAI rated site were carefully reviewed and analyzed by Merck and Dr. Honig, including a full audit of all the sites for that study conducted by Merck and a reanalysis of the study results based on the revised database. There were no significant differences noted between the two analyses. Further, the DSI auditor was provided with clinical data from the NDA by the medical reviewer that was compared to source data at the three audited sites. There were no discrepancies noted.

The one clinical site audited by DSI for NDA 20-830 received an NAI rating. The audit report was reviewed by Dr. Trontell who agreed that the deficiencies noted by the inspector were not of concern with regard to database integrity.

Based on the results of the DSI audits, and based on the limited auditing of the NDA performed by the two medial reviewers, there are no reasons to suspect any serious data integrity problems with the NDA databases.

Labeling

The trademark "Singulair" was reviewed by the Labeling and Nomenclature Committee and found to be acceptable. The trademark is also acceptable to the division. The package insert, carton, and container labeling are nearing completion. There are a few outstanding issues related to the representation of some of the clinical trial efficacy results that remain to be agreed between the agency and the sponsor. Otherwise the labeling had been reviewed by the various disciplines and has been found to accurately reflect the data submitted to the NDAs.

Conclusion

There are a few remaining labeling issues that need to be agreed to between the sponsor and the agency. Otherwise there are no outstanding issues and the sponsor should receive an APPROVAL letter for both NDAs. The sponsor will be reminded in the approval letter for NDA 20-830 of their commitment

The sponsor will also be strongly encouraged in the same action letter to pursue further

cc:

NDA 20-829

NDA 20-830

HFD-570 Division Files

HFD-570/Jenkins

HFD-570/Kuzmik

HFD-570/Honig

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-830

FEB 20 1998

Merck Research Laboratories
Sumneytown Pike
P.O. Box 4
West Point, PA 19486

Attention: William G. Roberts, M.D.
Director, Regulatory Affairs

Dear Dr. Roberts:

Please refer to your new drug application (NDA), dated and received February 21, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) Chewable Tablets.

We also refer to your submissions dated March 18, April 11, May 1, June 13, 17, and 19, July 3, 10, and 31, September 5, 23, and 29, October 14, 16, and 29, November 7, 13, 14, 18, 21, 25, and 26, and December 4 and 11, 1997, and January 13, 20, 26, and 28, and February 2, 3, 5, 6, 9, 12, and 20, 1998. The user fee goal date is February 21, 1998.

This new drug application provides for the use of Singulair Chewable Tablets for the prophylaxis and chronic treatment of asthma in pediatric patients ages 6 to 14.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling and patient package insert submitted on February 20, 1998, and mock-up carton and container labels submitted on November 25, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-830." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated February 2, 1998.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of the commitment in your annual report to this NDA. The status summary should include the number of patients entered in the study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to the Phase 4 commitment must be clearly designated "Phase 4 Commitment." The protocol for this study should be submitted within 3 months of the date of this letter and the study should be initiated within 6 months of the date of this letter.

We also strongly recommend that you pursue additional dose-ranging efficacy trials in pediatric patients to further evaluate the optimally effective pediatric dose and to validate your plans to use the pharmacokinetic dose extrapolation model for dose selection in the 2-5 year age group.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Pulmonary Drug Products and two copies of both the promotional material and the package insert directly to the following:

Food and Drug Administration
Division of Drug Marketing, Advertising,
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Within 30 days of the date of this letter, please submit a labeling supplement revising the PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy subsections, and OVERDOSAGE section so that the dosage comparison between humans and animals is based on plasma drug concentrations rather than body surface area.

If you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-829 Trade (generic) names Singulair (montelukast sodium) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&W studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Singular Tablets and Singulair Chewable Tablets are indicated for
adult and pediatric patients 6 years & older for the prophylaxis and
chronic treatment of asthma.

[Redacted area]

[Lined area for additional explanation]

ISI

Signature of Preparer

1/23/98

Date

cc: Orig NDA
HFD- /Div File
NDA Action Package