MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 618-96, 618-97
AVIDA 0.15 EC, ZEPHYRO 0.15 EC

FROM: William S. Woodrow WSW (2-11-91)
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

TO: G. LaRocca / Adam Heyward (PM13)
Insecticide + Rodenticide Branch
Registration Division (H75-05C)

APPLICANT: Merck & Co., Inc. Division of
Merck Sharp & Dohme Res. Labs.
Hillsborough Road
Three Bridges, N.J. 08887

FORMULATION FROM LABEL:

Active Ingredient(s):
Avermectin B1a mixture of avermectins containing
86% avermectin B1a (5-alpha-demethyl avermectin
A1a) and 14% avermectin B1b (5-alpha-demethyl
-25-d(1-methylpropyl)-26-(1-methyl ethyl)
Avermectin A1a)

Inert Ingredient(s): ......................

% by wt.

Total 100.0%
BACKGROUND

Machle & Co., Inc. submitted acute oral, two acute dermal toxicity, an acute inhalation, and a dermal sensitization study, to support registration of AVID 0.15 EC MITICIDE/INSECTICIDE (618-96), and ZEPHYR 0.15 EC MITICIDE/INSECTICIDE (618-97).

The formulations for AVID 0.15 EC and ZEPHYR 0.15 EC are identical, and acute toxicity data are submitted to support both products.

Previous reviews of acute toxicity data submitted to support Abamectin (Avermectin):

William Dykstra, Oct. 25, 1985

Abamectin (Avid) Tax Category

- acute oral LD50 > 5.0 g/kg IV
- acute dermal LD50 > 2.0 g/kg III
- acute inhalation LD50 > 1.062 mg/l III
- Eye irritation III
- Skin irritation III
- Derm. Sen. guinea pig negative
2.

William Dykstra  March 15, 1989

Toxicity:

- Acute oral: 25.0 g/kg
- Acute dermal: 7.0 g/kg
- Acute inhalation: LC50 = 1.02 mg/L
- Eye irritation = Corneal opacity: absent by day 14
- Skin irritation, cleared by day 7
- Dermal sensitization = not a dermal sensitizer

Note: Dykstra reviewed a new eye irritation study (3-15-89); MRID # 409125-01, Lab. #888-085-0, using "same formulation as Agrimek 0.15 EC."

Merk Sharp & Dohme changed the Avid 0.15 EC formulation to an alternative formulation, which is the same as the Agri-Mek 0.15 EC formulation.

The formulation changes:
George L. Roccia's letter to Merck (1-17-91) stated that the proposed change in formulation may alter the compound-related toxicity, and that therefore a complete battery of acute toxicity data will be required. The request for new toxic (acute) is based on Lucy Macken's observation that [redacted] can enhance penetration through skin by the subject pesticide.

RECOMMENDATION

1. The acute toxicity studies conducted with the alternate (new) product formulation (same as Agrimek 0.15 EC), that are acceptable include: the acute oral, acute dermal, and the acute inhalation studies.

2. One of the acute dermal studies and the termed sensitization study were not acceptable, and were graded supplementary:
   a. Acute dermal MRID # 420203-02, Lab # 11-91-2607. - One dose test results were < than 21 ml (2 gr/kg); LD50 not determined.
   b. Dermal sensitization MRID # 420203-04 (MRID) Lab No 11-91-685-0 - Dermal epicutaneous
stage of test (maximization test), patches
securing topically applied test mat, detached
from skin, thus precluding valid test
evaluation. (Tester stated compound ingredient
probably dissolved adhesive material, however 3
24-hour contact during acute dermal was
successful. NOTE: When it became apparent
that patches were insecure, double thickness
aluminium foil should have been placed
over patches, and around trunks of animals.
3) Current acute toxicity profile for Audi 0.15-
EC, Zephyr 0.15 EC (EPA Reg. Nos. 618-96, and
618-97, respectively):  

<table>
<thead>
<tr>
<th>Study</th>
<th>MRID Tax Category</th>
<th>Acute Oral LD50 = 304 mg/kg</th>
<th>420903-01</th>
<th>11 Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute dermal LD50 = 1.8 g/kg</td>
<td>420798-01</td>
<td>11 Guideline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute Inhalation LC50 = 3.5 mg/ll</td>
<td>420800-01</td>
<td>11 Minimum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute dermal &lt; 2.0 g/kg</td>
<td>420603-02</td>
<td>Supplementary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermal sensitization not determined</td>
<td>420603-04</td>
<td>Supplementary</td>
</tr>
</tbody>
</table>

((Note 4)) The acute inhalation study (MRID No. 420800-01), was
graded Cate Minimum Data: only mmad GSD values presented;
20 particles by Impactor plates and 90 cumulative particles
at and below each Impactor stage not presented.
5) The following acceptable acute toxicity studies conducted using the current Avito 0.15 EC formulation must be submitted:

- a. Skin irritation study, and
- b. Dermal sensitization study

LABELLING (both Avito 0.15 EC and Zephylo 0.15 EC)

1) The WARNING signal word is appropriate.
2) Change the Precautionary Statements as follows:

Causes substantial but temporary eye injury.
May be fatal if swallowed or absorbed through skin. Do not get in eyes, on skin, or on clothing. Wear goggles, face shield, or safety glasses. Wear protective clothing and rubber gloves. Harmful if inhaled. Avoid breathing dust (vapor or spray mist). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

3) Change the Statements of Practical Treatment as follows:
(Practical statements change)

11. If Swallowed: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

If on Skin: Wash with plenty of soap and water. Get medical attention.

If in Eyes: Flush with plenty of water. Call a physician.

If Inhaled: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention.

PM NOTE: Upon receipt of requested acute toxicity data, precautionary labeling may require revision.

PM NOTE: Both of the products presently being considered in this report (Zephyr 0.15EC Miteicide / Insecticide [618-97] and Avid 0.15EC Miteicide / Insecticide [618-96]) contain identical formulations. Both products are intended to control mites and insects. Both products are
supported by the same acute toxicity data. The product labels do indicate some differences in use/use patterns; however, one of these products is designated "restricted use only" - 618-97, while the other product use is not restricted - 618-96. PM should consider whether or not both these products should be considered for restricted use.
DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (3) 9-11-91
Reviewer: H. Walter
MRID No.: 420203-01
Report Date: 12-4-91
Author(s): W.V. Baedon
Report No.: TB91-2606
Species: Rat, Cr: CD (SD)
Age: 4 1/2 weeks
Weight: 128-135 g
Exposure: (1/4): other
Source: Charles River Lab., Raleigh, L-616,815-36Q-4 Spray Formulation
Test Material: MK-09 36 (Abamectin) - macrocyclic lactone dioxachloride
Quality Assurance (40 CFR §160.12): Yes (QA & GLP)
Conclusion:
Density (Av) = 960 g/mL
1. LD50 (mg/kg): Males = 2,919 mg/kg; Females = 2,92 mg/kg
2. The estimated LD50 is
3. Tox. Category: II
Classification: Guideline

Procedure (Deviations from §81-1):
Groups of 10 M + 10 F each were dosed by gastric intubation. Animals observed daily for mortality and clinical signs of toxicity for 14 days. Bodies examined days 0 + 14.

Results:

<table>
<thead>
<tr>
<th>DOSAGE (mg/kg)</th>
<th>NUMBER KILLED</th>
<th>NUMBER TESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0.25 mg/kg</td>
<td>1/10</td>
<td>0/10</td>
</tr>
<tr>
<td>0.40 mg/kg</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>0.64 mg/kg</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>1.02 mg/kg</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>1.63 mg/kg</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Clinical signs: Males: by day 20-25% less than control only by day 14 recovery to 10-15% less than control.
All rats died at 0.64, 1.02, and 1.63 mg/kg died beginning about day 2 to 2 1/2 hrs post dosing. Males dosed @ 0.4 mg/kg died 4 to 4 1/2 hrs post dosing. All rats had tremors, ataxia and/or bradypnea. Salivation, lacrimation,
Post-Mortem:

Frequent upper nose gape, gross observations included
stomach distended, of undulant mucosa brown, smeared, and
some egested mucosa green. Upper dive observations
included lungs: red font, red matting. Lower bowel
gross observation undied liver, red or white feces,
red urine, red eyest, red matting, and egested feces.
Summary:

1. LD50 (mg/kg): Males = __________; Females = __________
2. The estimated LD50 is > 1.8 g/kg
3. Tox. Category: II, Classification: Guideline

Procedure (Deviations From §81-2):

Hair was removed from back of 15 male rabbits with clippers; 10 x 10 cm area selected for study. 3 groups of 5 rabbits, separated with different doses of test material. Dose application to skin using syringe.

Results: Treated sites covered 4 x 4" gauge, secured with tape.

### Reported Mortality

<table>
<thead>
<tr>
<th>DOSAGE (g/kg)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>1.0 g/kg</td>
<td>0</td>
</tr>
<tr>
<td>1.4 g/kg</td>
<td>1/5</td>
</tr>
<tr>
<td>1.8 g/kg</td>
<td>1/5</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Treatment site then wrapped in clear polyethylene plastic for all animals during 24 hour exposure. Wrapping removed, site wiped. Animals checked frequently, day of treatment (during 24 hr exposure), 1, 2, 3, 7, 13, 14, 15, animals removed from cage and examined. Draining scaling used to evaluate dermal treatment site.
Body weights recorded days 0, 7, 15. All animals subjected to necropsy.

Results: 1 rabbit died at 1.85 kg, 1 died at 1.49 kg, and 1 at 1.00 kg.

Clinical: Decreased food intake, decreased activity, droopy ears - 3/10 @ 1.45 kg, 4/10 @ 1.85 kg. Note: formalin seen in all surviving animals. Decrease in body weight of 5% at high dose, 2% at low and moderate doses. On day 1, all but most of weight regained by day 5.

Necropsy: Tissue bleeding. Two male deaths due to inadequate weight in post-collar removal. Most rabbits exhibited skin scaling at application site. Remaining green charge observed believed not to be detrimental.
DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: 13-9-11-91  Reviewer: W. A. Weller
MRID No.: 420203-02  Report Date: 12-4-91
Testing Laboratory: Merck Inst. for Therapists
Author(s): W. J. Bazelon
Species: Rabbit, N 7, white, 36-37.6 kg. old
Sex: 5 males 5 females
Test Material: 5mL F-liquid, 5mL 2% vehicle
Summary: Density = 0.96 g/ml Estimation of LD50 not possible.

1. LD50 (mg/kg): Males =  ; Combined =  ; Females =
2. The estimated LD50 is < 2.1 ml (2.0 g/kg) (2000 mg/kg)
3. Tox. Category:  Classification: 

Procedure (deviations from §81-2): Hair was removed from back of 8mL & 8 females to expose an 10x10 cm area. Test material (2.1ml) applied to clipped area or back of 5mL & 5 females. 2.1ml vehicle alone applied to similar area on back of 3mL & 3 females.

Results: Treated sites covered with clear plastic & secured. Reported Mortality

<table>
<thead>
<tr>
<th>DOSAGE (mL/kg)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>2.1 mL/kg (test) (mL-0936)</td>
<td>4/5</td>
</tr>
<tr>
<td>2.1 mL vehicle alone (control)</td>
<td>0/3</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Plastic collars placed on each rabbit. Dressings removed after 24 hours. Residual test material wiped off. Each rabbit examined for signs of toxicity and mortality. Treated sites examined daily according to Draize: Bulging recorded deep 0.7 x 14.
Clinical: No systemic signs first were noted. Appox 1-4 hrs after initial removal, atopic, hives, itching, sneezing,流泪, sneezing, scratching, and death (5 animals) seen in test group. 6 th rabbit dead in Bog 2. Remaining 2 rabbits appeared normal except for no systemic effects noted in vehicle treated animals.

Necropsy: (Test animals)

Examination of animals: Epidermis application site:书店 or diffuse brown/red discoloration with or without scaling. Overall grade ranged from moderate (4/6) to mild (2/6) skin damage.

Terminated necropsy: prominent scaling at application site, crust formation, epidermal thickening, granulation. No other gross findings.
DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (13) 8-15-91 Reviewer: W. Woodrow
MRID No.: 420800-01 Source: Report Date: 12-5-91
Testing Laboratory: Bio-Research Labs Quebec Report No. 77491-9001
Author(s): R. Labes
Species: R. Spenorl, Dauder Weight: 28.3-37.2 g, 17.5-22.9 g
Sex: 96.1 cm 80.5 cm
Source: Charles River, Canada
Test Material: MK-0736E (Abamectin 0.15 EC, batch 05)
Quality Assurance (40 CFR §160.12): Yes (QA - 160.12)

Summary:

1. LC50 (mg/kg): Males = 3.9 (3.5-4.3) mg/L; Females = 3.1 (2.9-3.4) mg/L; Combined = 3.5 (3.2-3.8) mg/L
2. The estimated LC50 is ______.
3. Mean Concentration: ______.
4. Tox. Category: III. Classification: Minimum

Procedure (Deviations From §80-2): All animals acclimated for 2 weeks prior to test. Groups of 10 males exposed for 4 hours to test material doses, or to vehicle or air alone (controls). All animals observed 2 x

Results:

<table>
<thead>
<tr>
<th>Exposure Concentration (mg/L)</th>
<th>Reported Mortality</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>2.77 mg/L (low dose)</td>
<td>0/10</td>
<td>2/10</td>
</tr>
<tr>
<td>3.11 mg/L (medium dose)</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>3.41 mg/L (upper medium dose)</td>
<td>5/10</td>
<td>8/10</td>
</tr>
<tr>
<td>4.06 mg/L (high dose)</td>
<td>5/10</td>
<td>8/10</td>
</tr>
<tr>
<td>Air control</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Low vehicle control</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>High vehicle control</td>
<td>0/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Daily for mortality and moribundity. Body weights were recorded on day 0, and on days 1, 2, 3, 6, and 13 and 14. Complete necropsies were performed on all animals. Exposures were more only volume.
A 3.1 liter Pyrex beaker positioned in restraint cone. Exposure tube chamber contained port next breathing distance for air sample removed. Air flow through chamber 30 L/min., 20-24°C, 30-70% R.H. Test of control atmosphere generated using a single jet atomizer supplied with filtered air. Chamber flow controlled by varying rate of aerosol delivery to chamber. The aerosol (not less than 10 µm air) through chimney mg/L) and the aerosol chamber concentration measured using gravimetric means. Macerated filter weights L air sampled mg/L air. The particle size distribution was determined using an Anderson 10CFCM Cascade Impactor. MMAD and GSD calculated.

Results: Chamber Concentration - Avg. of 4 samples:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Air control</td>
<td>0.0000 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>Low vehicle</td>
<td>2.7405 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>High vehicle</td>
<td>3.8847 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>Low dose</td>
<td>2.2771 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>3.1147 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>Upper dose</td>
<td>3.4124 mg/L</td>
<td>100</td>
</tr>
<tr>
<td>High dose</td>
<td>4.0634 mg/L</td>
<td>100</td>
</tr>
</tbody>
</table>

Chamber concentration values (means of 4 samples), measured gravimetrically, as mentioned above.
Particle size analysis:

Note: The fraction (%) of particles collected by each cascade impactor stage, according to size range, was not reported. Also, the cumulative % of particles, including and below each size range of the impactor(s), was not reported; only mean and G. S. D. values reported.

<table>
<thead>
<tr>
<th>Dose</th>
<th>MMAD</th>
<th>GSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vehicle control</td>
<td>2.7 μm ± 2.2</td>
<td></td>
</tr>
<tr>
<td>High vehicle control</td>
<td>2.3 μm ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>2.3 μm ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Lower int. dose</td>
<td>2.1 μm ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Upper int. dose</td>
<td>2.2 μm ± 2.2</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>2.0 μm ± 2.2</td>
<td></td>
</tr>
</tbody>
</table>

All treated and control animals showed body weight loss post exposure; weight losses were recorded and survivors body weights recorded to the study termination.

Clinical signs: tremors, cold body temperature, lethargy, lack of balance, pallor, transient staining of muzzle or rectal region.
DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (13) 9-13-91 Reviewer: 
MRID No.: 420-03-04 Report Date: 9-13-91
Testing Laboratory: Merck Sharp & Dohme Report No. T7891-638-0
Author(s): G. Durand-Cavagna
Species: guinea pig, Hartley
Sex: F Weight: 300-350g
Source: Charles River, France
Test Material: MK-0936 EC 0.15%
Positive Control Material: 2-amino-4-chlorobenzene (DNCB)
Method: Magnusson & Kligman (modified)

Summary:
1. This product is not a dermal sensitizer. (not determined)
2. Classification: supplementary

Procedure (Deviation from §81-6): Testers state that "this test procedure has been modified previously with dinitrochlorobenzene and other positive agents."

Solutions employed:

Results: 10 (day 1) vehicle blank EC or MK-0936 0.15 EC 1/10 equal volumes of Freund's Complete Adjuvant. For epicutaneous applications (day 5-9), the vehicle blank EC or MK-0936 0.15 EC were applied at 1% dilution. For epicutaneous applications on day 22 (challenge) the vehicle blank EC or MK-0936 0.15 EC were applied with an equal volume of distilled water.

Treatment groups:

Ten females control group.
11 females in vehicle blank EC group.
11 females in MK-0936 0.15 EC group.

A preliminary screen was conducted to determine
Concentration of test vehicle materials to use in main test: 0.15 mL MK-0936 0.15 EC or 0.15 mL of vehicle blank EC were irritating. 0.15 mL of MK-0936 0.15 EC diluted with an equal volume of distilled water was not irritating.

Induction:

1) Control group = Freund's Complete Adjuvant
   Diluted with an equal vol. of distilled water.

2) Vehicle blank EC Group = Vehicle diluted with an equal volume of Freund's Complete Adjuvant.
   MK-0936 0.15 EC group = MK-0936 0.15 EC diluted with an equal volume of Freund's Complete Adjuvant.

Topical: on day 7, irritant acapella were applied (days 8-17) and pre-treated efficaciously with approximately 40 mg of 10% sodium lauryl sulfate in polysorbate. 

Day 8-17, 0.075 mL of following placed over the intra dermal injection site.

Control group: 2 x 0.075 mL saline.

Vehicle group: 2 x 0.075 mL vehicle blank EC.

MK-0936 0.15 EC group: 2 x 0.075 mL of MK-0936 0.15 EC.

Note: During concentration screen preliminary, 0.2 mL MK-0936 0.15 EC applied efficaciously.
for 48 hrs. Control patches. However, patches were
removed, primarily due to disking properties.

At 12 weeks—consequently both formulations were
applied without patches on Day 8x9 (0.075 ml)
on each day. This amount (0.075 ml) is very small
and probably evaporated and or became subject
absorbed. On the other hand, the topical
application of 1% dextran have been covered with
patches for the full 48 hours in order for
the test to be accurate.

Challenge: Day 22, two areas clipped on the
right and left flanks of all animals. 
Vehicle: Blank 0.1% of dextrose.

Right flanks - saline + patch (negative)
Left flanks - vehicle, or MK-0936 0.15 EC
(2 x 2 cm patch)

Central group

7x3 patches, (Whitman filter paper) containing
0.15 ml saline (right flanks), 2x3 patches
containing either 0.15 ml Vehicle Blank
(left posterior flanks) or 0.15 ml MK-0936 0.15 EC
(left posterior flanks) diluted 1:1 equal vol.

Patches removed with tape for 24 hrs (other
removal...
Challenge sites read at 2.4 and 4.8 hours after patch removed. Scoring scale 0-3

**Control Group (not induced)**

<table>
<thead>
<tr>
<th>Score</th>
<th>24 hr 2.48 hr right anterior flank, saline</th>
<th>0.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>left</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>left, posterior in MK-0936 0.15% BC, V10 24 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/10 @ 48 hrs.</td>
<td></td>
</tr>
</tbody>
</table>

**Vehicle Blank BC Group (not induced)**

<table>
<thead>
<tr>
<th>Score</th>
<th>24 hr 48 hrs. right flank, saline</th>
<th>0.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 hrs Vehicle Blank BC in MK-0936 0.15% BC, V10</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>48 hrs</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**MK-0936 0.15% BC Group (induced)**

<table>
<thead>
<tr>
<th>Score</th>
<th>24 hr 48 hrs. right flank, saline</th>
<th>0.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 hrs. Left in MK-0936 0.15% BC, V10</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>48 hrs.</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Conclusion: It would appear that it is impossible to distinguish the control group results from the animal results from induced animals (induced with test material) lack of assurance that test material maintained in contact with test site for the prescribed 48 hours.