

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Rubber Panel T.R.U.E. TEST® safely and effectively. See full prescribing information for Rubber Panel T.R.U.E. TEST.

Rubber Panel T.R.U.E. TEST
Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test
Patch, for Topical Use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

Rubber Panel T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis in persons 6 years of age and older whose history suggests sensitivity to one or more of the 5 substances included on the Rubber Panel T.R.U.E. TEST. (1)

DOSAGE AND ADMINISTRATION

- For topical use only.
Apply the adhesive panel of allergens and allergen mixes on healthy skin of the back. Remove panels and evaluate the skin 48 hours after application. Re-evaluate the skin 72 to 96 hours after application. (2)

DOSAGE FORMS AND STRENGTHS

One adhesive panel consisting of 5 allergen and allergen mix patches and a negative control.

CONTRAINDICATIONS

- Do not apply to skin of patients with a history of severe allergic reaction (systemic and/or local) to any of the allergen components or inactive substances of Rubber Panel T.R.U.E. TEST. (4)

- Do not apply to skin that is injured or inflamed. (4)

WARNINGS AND PRECAUTIONS

- Acute allergic reactions, including anaphylaxis, may occur. (5.1)
- Sensitization to one or more of the allergens may occur with initial or repeat testing. (5.2, 5.9)
- Extreme positive reactions, excited skin syndrome, tape reactions, irritant contact dermatitis, persistent reactions, and late reactions at the test site may occur. (5.3, 5.4, 5.5, 5.6, 5.7, 5.8)

ADVERSE REACTIONS

The most common adverse reactions (occurring in more than 1% of the study population) were erythema, pruritus, dermatitis flare, hyperpigmentation and tape irritation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SmartPractice at 1-800-878-3837 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Patients on systemic or topical immunosuppressant therapy may have a diminished reaction to Rubber Panel T.R.U.E. TEST. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Rubber Panel T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older whose history suggests sensitivity to one or more of the 5 substances included on the Rubber Panel T.R.U.E. TEST.

2 DOSAGE AND ADMINISTRATION

- For topical use only

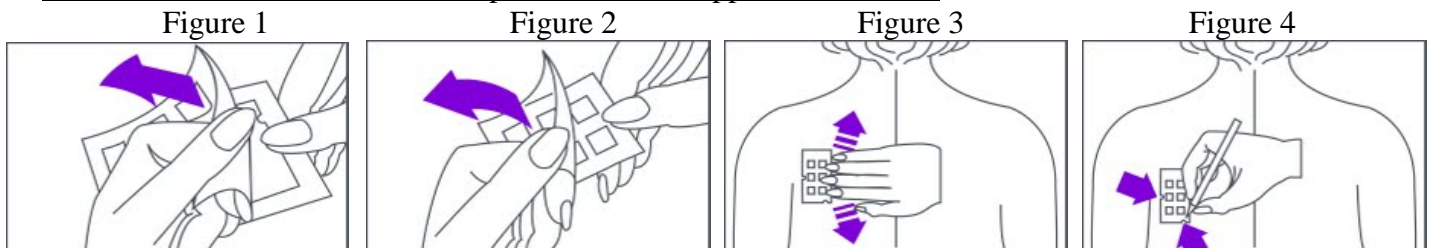
Rubber Panel T.R.U.E. TEST contains one adhesive panel consisting of 5 allergen and allergen mix patches and a negative control. See *Description (11)* for allergen types and amounts.

2.1 Application Instructions

Rubber Panel T.R.U.E. TEST should only be applied to healthy skin. Test sites should be free of scars, acne, dermatitis, or other conditions that may interfere with test result interpretation. Avoid application of Rubber Panel T.R.U.E. TEST panel to recently tanned or sun-exposed skin because this may increase the risk of false negatives. Avoid patch testing on patients for three (3) weeks after ultraviolet (UV) treatments, heavy sun, or tanning bed exposure. Avoid using alcohol or other irritating substances on the skin prior to testing. Avoid excessive sweating during the testing period to maintain sufficient adhesion to the skin. Avoid excessive physical activity to maintain sufficient adhesion and to prevent actual loss of patch test material. Avoid getting the panels and surrounding area wet.

If excessive body hair exists at the test site, remove with an electric shaver (do not use razors). Very oily skin may be cleaned with mild soap and water prior to testing.

The Rubber Panel T.R.U.E. TEST panel should be applied as follows:



1. Peel open the package and remove the test panel (Figure 1).
2. Remove the protective plastic covering from the test surface of the panel (Figure 2). Be careful not to touch the test substances.
3. Position the test panel on the patient's back as shown in Figure 3. Allergen number 1 should be in the upper left corner. Avoid applying the panel on the margin of the scapula or directly over the midline of the spine. Ensure that each patch of the allergen panel is in contact with the skin by smoothing the panel outward from the center to the edge (as illustrated in Figure 3).
4. With a medical marking pen, indicate on the skin the location of the two notches on the panel (as illustrated in Figure 4).
5. If needed, hypoallergenic surgical tape, appropriate for patch testing, may be used for increased adhesion around the outside edges of the panel.

2.2 Timing of Test Readings

Schedule patients to return approximately 48 hours after patch test application to have the panel removed. Prior to removal of the panel, use a medical marking pen to remark the notches found on the panel. The patch test reaction on the patient's skin may be evaluated at 48 hours, but an additional reading(s) at 72 and/or 96 hours is necessary. Late positive reactions may occur 7 to 10 days after application of the panels. Patients should be advised to report these reactions to you. Late positive reactions, occurring more than 14 days after application of the panels, may be indicative of active sensitization [See *Warnings and Precautions (5.2)*].

2.3 Interpretation Instructions

An identification template is provided for the panel for quick identification of any allergen that causes a reaction. To assure correct positioning, marks on the skin made with the medical marking pen should correlate with the notches on the template. The interpretation method, similar to the one recommended by the International Contact Dermatitis Research Group, is as follows:

- ? Doubtful reaction: faint macular erythema only
- + Weak positive reaction: non-vesicular with erythema, infiltration, possibly papules
- ++ Strong positive reaction: vesicular, erythema, infiltration, papules
- +++ Extreme positive reaction: bullous or ulcerative reaction
- Negative reaction
- IR Irritant reaction: Pustules as well as patchy follicular or homogeneous erythema without infiltrations are usually signs of irritation and do not indicate allergy.

Itching is a subjective symptom that is expected to accompany a positive reaction.

False Negatives

False negative results may be due to insufficient patch contact with the skin and/or premature evaluation of the test. Repeat testing may be indicated. The effect of repetitive testing with Rubber Panel T.R.U.E. TEST is unknown [See *Warnings and Precautions (5.9)*].

False Positives

A false positive result may occur when an irritant reaction cannot be differentiated from an allergic reaction. A positive test reaction should meet the criteria for an allergic reaction. If an irritant reaction cannot be distinguished from a true positive reaction or if a doubtful reaction is present, a retest may be considered. The effect of repetitive testing with Rubber Panel T.R.U.E. TEST is unknown [See *Warnings and Precautions (5.9)*].

3 DOSAGE FORMS AND STRENGTHS

Rubber Panel T.R.U.E. TEST contains one (1) adhesive panel consisting of 5 allergen and allergen mix patches and a negative control. [See *Description (11)* for allergen types and amounts].

4 CONTRAINDICATIONS

Do not apply to skin of patients with a history of severe allergic reaction (systemic and/or local) to any of the allergen components or inactive substances of Rubber Panel T.R.U.E. TEST [See *Description (11)*].

Do not apply to skin that is injured or inflamed.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Allergic Reactions

Acute allergic reactions, including anaphylaxis, may occur. Appropriate medical treatment must be available in case of an acute allergic reaction, including anaphylaxis, following the application of Rubber Panel T.R.U.E. TEST. If a severe allergic reaction occurs, remove the Rubber Panel T.R.U.E. TEST panel and initiate treatment. Immediate contact urticaria may present within minutes to an hour after application in patients who are pre-sensitized to some allergens and may be local or generalized. Patients may be advised to remove the panel themselves if they experience systemic symptoms [See *Patient Counseling Information (17)*].

5.2 Sensitization

A negative patch test reaction, followed by a positive reaction 10 to 20 days after panel application, may indicate active sensitization. Active sensitization is confirmed upon retesting with a positive reaction occurring at the 72 and/or the 96 hour reading. If patients undergo a second series of patch tests immediately, select a new test site for Rubber Panel T.R.U.E. TEST application. Alternatively, the same site may be retested after a 3-week clearing period, provided the site remains free of conditions that might affect test results [See *Dosage and Administration (2.1)*]. The safety and effectiveness of repetitive testing with Rubber Panel T.R.U.E. TEST is unknown [See *Warnings and Precautions (5.9)*].

5.3 Extreme Positive Reactions

Extreme positive (++++) reactions that are bullous or ulcerative with pronounced erythema, infiltration, and coalescing vesicles may present in extremely sensitive patients [See *Dosage and Administration (2.3)*].

5.4 Excited Skin Syndrome (Angry Back)

Excited skin syndrome is a regional state of skin hyper-reactivity caused by the presence of a strong positive reaction which may result in other patch test sites to become reactive.

5.5 Tape Reactions

Reactions to the Rubber Panel T.R.U.E. TEST tape or adhesive may occur. Rubber Panel T.R.U.E. TEST panel tape and the individual patches are composed of polyester. The adhesive used in the panel is acrylate-based and processed to remove free monomers that may be allergenic [See *Description (11)*].

5.6 Irritant Contact Dermatitis

Patients may experience irritant contact dermatitis upon exposure to any of the allergens contained within Rubber Panel T.R.U.E. TEST that cause direct damage to the skin at the test site. Recurrence of an irritant response is not limited to exposure to the specific substance, but may follow exposure to any chemical irritants.

5.7 Persistent Reactions

Positive reactions may persist from 7 days to months after panel application.

5.8 Late Reactions

Late positive reactions may occur 7 to 10 days after application of the panel.

5.9 Repeat Testing

The safety and efficacy of repetitive testing with Rubber Panel T.R.U.E. TEST is unknown. Sensitization or increased reactivity to one or more of the allergens may occur [See *Warnings and Precautions (5.2)*]. If patients undergo a second series of patch tests immediately, select a new test site for Rubber Panel T.R.U.E. TEST application. Alternatively, the same site may be retested after a 3-week clearing period, provided the site remains free of conditions that might affect test results [See *Dosage and Administration (2.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in clinical practice. Data from clinical trials evaluating T.R.U.E. TEST containing the rubber allergen(s) of the same concentration and formulation support the safety of Rubber Panel T.R.U.E. TEST.

Adults

Table 1 presents a summary of clinical trials conducted in North America and Europe of T.R.U.E. TEST containing rubber allergens.

Table 1- Overview of Clinical Trials of T.R.U.E. TEST Containing Rubber Panel Allergens Among Adults 18 Years of Age and Older (Studies 1-5)

Clinical Study Overview		Study 1 N ^a =127	Study 2 N ^a =121	Study 3 N ^a =119	Study 4 N ^a =50	Study 5 N ^a =49	Total N ^a =466
Age Range (years)		19-79	18-77	19-76	19-82	18-68	18-82
Sex (% female)		68%	68%	73%	72%	98%	72%
Ethnicity	Caucasian	86%	88%	83%	92%	98%	87%
	Black	9%	12%	11%	4%	0%	12%
	Other	5%	1%	6%	4%	2%	1%
Allergens	Carba mix		X	X	X		
	Black Rubber Mix		X	X	X		
	Mercapto Mix		X	X	X		
	Thiuram Mix	X		X	X	X	
	Mercaptobenzothiazole		X	X	X		

N^a= Number of adult subjects in the study

The most common adverse reactions (occurring in more than 1% of the adult study population) were erythema, pruritus, hyperpigmentation and tape irritation. Table 2 summarizes the adverse reactions to allergens found on Rubber Panel T.R.U.E. TEST. Subjects' adverse reactions were recorded on case report forms by study personnel. Adverse reactions were recorded during subject follow up visits, which varied between 24 and/or 96 hours and/or day 21. [See *Clinical Studies (14)*].

Table 2- Summary of Adverse Reactions Reported Among Adults 18 Years of Age and Older (Studies 1-5)

	Black Rubber Mix N ^a =290 n ^b (%)	Carba Mix N ^a =290 n ^b (%)	Mercaptobenzothiazole N ^a =290 n ^b (%)	Mercapto Mix N ^a =290 n ^b (%)	Thiuram Mix N ^a =345 n ^b (%)
Erythema	2 (0.7)	0 (0.0)	2 (0.7)	3 (1.0)	1 (0.3)
Hyperpigmentation	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)	2 (0.6)
Pruritus	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)	4 (1.2)

N^a= Total number of adult subjects in studies 1-5 tested with the specified allergen

n^b=Total number of adult subjects with available data for the events listed for the specified rubber allergen

Irritation to the tape contained within T.R.U.E. TEST products was reported in 3 of the 5 clinical trials. Tape irritation is not attributable to a specific allergen(s) and was reported as follows in Table 3:

Table 3- Tape Irritation Following Removal of T.R.U.E. TEST Patch Test Panels in Adults 18 Years of Age and Older (Studies 1-5)

Study 1 N ^a = 127 n ^b (%)	Study 2 N ^a =121 n ^b (%)	Study 3 N ^a =119 n ^b (%)	Study 4 N ^a =50 n ^b (%)	Study 5 N ^a =49 n ^b (%)
4 (3.1)	NR ^c	2 (1.7)	1 (2.0)	NR ^c

N^a= Number of adult subjects in the specified study

n^b= Number of adult subjects in the specified study reporting tape irritation

NR^c= Not reported

Panel Adhesion: Problems with panel adhesion were observed during some of the clinical studies. Poor panel adhesion was defined as any panel that fell off prior to the 48-hour removal time or as any test panel that was not in good contact with the skin or if one or more of the patch test allergens were not in good contact with the skin as evidenced at the time of panel removal at 48 hours. If the panel fell off the back prior to the 48-hour removal time, the subject was excluded from the efficacy calculations but not from the safety analysis. Over all studies, poor panel adhesion occurred 33 times (7.1%) (Table 4). In study 2, the poor adhesion was attributed to the particular lot of adhesive used to manufacture the clinical test tape.

Table 4- Incidence and Percentage of Poor Panel Adhesion of T.R.U.E. TEST Among Adults 18 Years of Age and Older (Studies 1-5)

	Study 1 N ^a = 127 n ^b (%)	Study 2 N ^a =121 n ^b (%)	Study 3 N ^a =119 n ^b (%)	Study 4 N ^a =50 n ^b (%)	Study 5 N ^a =49 n ^b (%)	Combined N ^a =466 n ^b (%)
Poor Adhesion ^c	0 (0.0)	14 (11.6)	2 (1.7)	5 (10.0)	12 (24.5)	33 (7.1)

N^a= Number of adult subjects in the specified study

n^b=Number of adult subjects in the study with available data for poor adhesion of the panel(s)

^c Poor adhesion was defined as any panel that fell off prior to the 48-hour removal time or as any test panel that was not in good contact with the skin or if one or more of the patch test allergens were not in good contact with the skin as evidenced at the time of panel removal at 48 hours.

Children and Adolescents 6 through 17 Years of Age

In an open-label, prospective, single-center study (NCT 00795951) conducted in the U.S., 102 children and adolescents 6 through 17 years of age with suspected allergic contact dermatitis had three T.R.U.E. TEST panels (Panels 1.1, 2.1 and 3.1) applied to their back or upper arm (study 6). The T.R.U.E. TEST panels contained 28 allergens of which 5 were rubber allergens/allergen mixes. The mean and standard deviation (STD) age of enrolled subjects was 11.6 (3.6) years. The study included comparable proportions of females and males (52.0% and 48.0%, respectively). The enrolled study population included 28 subjects (27.5%) 6 to 8 years of age, 29 subjects (28.4%) 9 to 12 years of age, and 45 subjects (44.1%) 13 to 18 years of age. Among all subjects, the most commonly reported form of dermatitis was allergic (97.1%), and the majority of subjects (99.0%) presented with symptoms of dermatitis at the time of entry into the study (usually on the arms and/or hands and the legs and/or feet).

The safety of patch testing with the three T.R.U.E. TEST panels was evaluated based on the frequency of adverse reactions, serious adverse events, and deaths for 21 days after patch application. Adverse events were graded as follows: mild (minimal symptoms or discomfort; does not interfere with function), moderate (discomfort requiring medication for relief; interferes with function), severe (symptoms interfere with function). Of 102 subjects who received the T.R.U.E. TEST panels, 8 (7.8%) adverse reactions were associated with the allergens contained in the Rubber Panel T.R.U.E. TEST (black rubber mix (n=1), carba mix (n=6) and thiuram mix (n=1)). Most of these reported adverse reactions (n=7) were mild, while one adverse reaction (dermatitis flare) was moderate in severity. The most commonly reported adverse reaction attributed to the Rubber Panel T.R.U.E. TEST allergens was dermatitis flare (n=7). One participant with a history of atopic dermatitis had a mild rash extending from a positive reaction to carba mix that resolved with topical corticosteroid treatment within 21 days after patch application.

Tape irritation was reported in 71 (70.3%) of the subjects. No late or persistent reactions were reported to any of the Rubber Panel T.R.U.E. TEST allergens. (A late reaction is defined as a reaction appearing for the first time at 7-10 days after application of the patch test. A persistent reaction is defined as a reaction that appears initially within 7 days of patch test placement and persists for 7-21 days after patch test placement.) No subject was discontinued from the study due to an adverse event. No serious adverse events or deaths were reported for 21 days after patch application.

Panel Adhesion: Data on adhesion of T.R.U.E. TEST panels for children and adolescents from study 6 are shown in Table 5.

Table 5- Panel Adhesion^a in Children and Adolescents 6 through 17 Years of Age (Study 6^b)

	T.R.U.E. TEST	T.R.U.E. TEST	T.R.U.E. TEST
	Panel 1.1	Panel 2.1	Panel 3.1
Adhesion	N ^c =100	N ^c =100	N ^c =100
	n ^d (%)	n ^d (%)	n ^d (%)
Excellent	71 (71.0)	72 (72.0)	82 (82.0)
Good	19 (19.0)	19 (19.0)	14 (14.0)
Fair	8 (8.0)	9 (9.0)	3 (3.0)
Poor	2 (2.0)	0 (0.0)	1 (1.0)
Test panel fell off	0 (0.0)	0 (0.0)	0 (0.0)

^a=Panel Adhesion was defined as follows:

Excellent = good skin contact and all tape edges adherent

Good = skin contact acceptable, some tape edges loose

Fair = skin-to-panel contact variable, tape edges lifting

Poor = little to no skin contact with panel

^b=Open label, prospective study conducted in the U.S. (NCT- 00795951)

N^c = Number of subjects with available data for the specified panel

n^d=Number of subjects with available data for adhesion for the specified panel

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of T.R.U.E. TEST in adults (which includes allergens on the Rubber Panel T.R.U.E. TEST). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to T.R.U.E. TEST product exposure.

- Acute allergic reactions [See *Warnings and Precautions (5.1)*]
- Extreme positive reactions [See *Warnings and Precautions (5.3)*]
- Excited skin syndrome (Angry back) [See *Warnings and Precautions (5.4)*]
- Irritant contact dermatitis [See *Warnings and Precautions (5.6)*]

7 DRUG INTERACTIONS

7.1 Systemic Antihistamines

The effect of concomitant systemic antihistamine administration on the performance of patch testing with Rubber Panel T.R.U.E. TEST is unknown.

7.2 Systemic Cyclosporins

The effect of concomitant or prior systemic cyclosporin administration on the performance of patch testing with Rubber Panel T.R.U.E. TEST is unknown.

7.3 Systemic Glucocorticoids

Oral steroids may cause false negative results of patch testing with Rubber Panel T.R.U.E. TEST. The risk of discontinuing or decreasing the dose of oral corticosteroids in order to perform the patch test must be weighed against the benefits of patch testing.

7.4 Topical Immunosuppressants and Immunomodulators

Avoid using test sites to which topical glucocorticoids, antihistamines, immunosuppressants, or immunomodulators are applied. The use of topical steroids or immunosuppressants at or near potential test sites should be avoided from at least one week prior to patch testing through the conclusion of patch testing.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with Rubber Panel T.R.U.E. TEST. It is also not known whether Rubber Panel T.R.U.E. TEST can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Rubber Panel T.R.U.E. TEST should be applied to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether any of the allergens in Rubber Panel T.R.U.E. TEST are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Rubber Panel T.R.U.E. TEST is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Rubber Panel T.R.U.E. TEST have not been established in persons younger than 6 years of age.

8.5 Geriatric Use

Clinical studies of Rubber Panel T.R.U.E. TEST did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Rubber Panel T.R.U.E. TEST (Rubber Panel Thin-layer Rapid Use Epicutaneous Patch Test) is a ready-to-use allergen patch test system consisting of 5 allergen and allergen mix patches and a negative control.

Each test consists of the following:

Panel- The panel consists of a piece of surgical tape (5.2 x 13.0 cm), each with 6 polyester patches of approximately 0.81 cm². Each patch is coated with a film containing a uniformly dispersed specific allergen or allergen mix. The negative control is an uncoated polyester patch.

Tape- The panel tape is composed of polyester. The adhesive used in the panels is acrylate-based. There is no natural rubber latex, rubber components, balsams or rosins in the adhesive or tape. Acrylate adhesives are processed to remove free monomers that may be allergenic.

Foil Pouch- Each test panel is covered by a protective sheet and sealed in a pouch of laminated foil.

Desiccant- A desiccant paper is included in the foil pouch for stability purposes.

Inactive Ingredients- The allergens are homogenized in one or more of the following materials to produce the allergen films that coat the patches: hydroxypropyl cellulose (HPC) and povidone (PVP).

The individual components of the Rubber Panel T.R.U.E. TEST Panel are listed below along with a quantitative description of each patch formulation.

Allergens on Rubber Panel T.R.U.E. TEST

Negative Control (Position 1):

The negative control is an uncoated polyester patch.

Carba Mix (Position 2):

Carba mix contains three chemicals used to stabilize rubber products: diphenylguanidine (purity $\geq 96\%$), zincdibutyldithiocarbamate (purity $\geq 96\%$), and zincdiethyldithiocarbamate (purity $\geq 96\%$) in equal parts. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 250 mcg/cm² of carba mix, which corresponds to 203 mcg of carba mix per patch. These chemical stabilizers and accelerators are found in many rubber products, pesticides, and some glues.

Black Rubber Mix (Position 3):

Black rubber mix contains the antioxidant and antiozonate chemicals N-isopropyl-N'-phenyl paraphenylenediamine (purity $\geq 95\%$), N-cyclohexyl-N'-phenyl paraphenylenediamine (purity $\geq 90\%$), and N, N'-diphenyl paraphenylenediamine (purity $\geq 90\%$) in the ratio 2:5:5. The gel vehicle is povidone. The product is formulated to contain 75 mcg/cm² of black rubber mix, which corresponds to 61 mcg of black rubber mix per patch. The components of black rubber mix are found in almost all black rubber products, such as tires, handles, and hoses.

Mercaptobenzothiazole (Position 4):

Mercaptobenzothiazole (purity $\geq 98.5\%$) is a vulcanization accelerator used in rubber products. The gel vehicle is povidone. The product is formulated to contain 75 mcg/cm² of mercaptobenzothiazole, which corresponds to 61 mcg of mercaptobenzothiazole per patch. This chemical is found in many rubber products, some adhesives, and is used as an industrial anticorrosive agent.

Mercapto Mix (Position 5):

Mercapto mix is composed of three chemical accelerators that are benzothiazole sulfenamide derivatives. N-cyclohexylbenzothiazyl-sulfenamide (purity $\geq 85\%$), dibenzothiazyl disulfide (purity $\geq 97\%$), and morpholinylmercaptobenzothiazole (purity $\geq 85\%$) are present in equal parts. The gel vehicle is povidone. The product is formulated to contain 75 mcg/cm² of mercapto mix, which corresponds to 61 mcg of mercapto mix per patch. This group of chemicals is found in many rubber products, such as shoes, gloves, and elastics.

Thiuram Mix (Position 6):

Thiuram mix is composed of four substances in equal parts: tetramethylthiuram monosulfide (purity $\geq 95\%$, contains small amounts of tetramethylthiuram disulfide); tetramethylthiuram disulfide (purity $\geq 95\%$, contains small amounts of tetramethylthiuram monosulfide); disulfiram, USP (tetraethylthiuram disulfide, purity $\geq 98.0\%$); and dipentamethylenethiuram disulfide (purity $\geq 95\%$, impurities unknown). The components of thiuram mix can chemically interact, resulting in the formation of mixed disulfides. Thiuram monosulfides and disulfides are the active allergens. The gel vehicle is povidone. The product is formulated to contain 27 mcg/cm² of thiuram mix, which corresponds to 22 mcg of thiuram mix per patch (5.5 mcg of tetramethylthiuram monosulfide, 5.5 mcg of tetramethylthiuram disulfide, 5.5 mcg of disulfiram, and 5.5 mcg of dipentamethylenethiuram disulfide). These antimicrobial, accelerator, and antioxidant substances are found in many rubber products.

12 CLINICAL PHARMACOLOGY

A positive response to Rubber Panel T.R.U.E. TEST is a classic delayed cell-mediated hypersensitivity reaction (type IV), which normally appears within 9 to 96 hours after exposure. Following primary contact, an allergen penetrates the skin and binds covalently or non-covalently to epidermal Langerhans cells. The processed allergen is presented to helper T-lymphocytes, resulting in inflammation that produces a papular, vesicular, or bullous response with erythema and itching at the site of application.

14 CLINICAL STUDIES

Data from clinical trials evaluating T.R.U.E. TEST containing the rubber allergen(s) of the same concentration and formulation support the effectiveness of Rubber Panel T.R.U.E. TEST.

A basic description of the interpretation method used by study personnel to evaluate the allergens contained in Rubber Panel T.R.U.E. TEST obtained during the clinical studies is as follows [See *Dosage and Administration (2)*]:

?	Doubtful reaction
+	Weak positive reaction
++	Strong positive reaction
+++	Extreme positive reaction
-	Negative reaction
IR	Irritant reaction

14.1 Adults

Five (5) studies of T.R.U.E. TEST conducted in adults in North America and Europe evaluated the frequency of patch reactions to allergens found on Rubber Panel T.R.U.E. TEST. Subjects ranged in age from 18 through 82 years. Subjects with suspected allergic contact dermatitis, based on history or clinical signs, were tested in all studies. [See *Adverse Reactions (6.1)*].

Study No. 1

This study evaluated the efficacy of T.R.U.E. TEST Panel 1.1, which includes one of the Rubber Panel T.R.U.E. TEST allergens (thiuram mix). A total of 127 subjects with suspected contact dermatitis were recruited. T.R.U.E. TEST Panel 1.1, containing 12 allergens (no negative control was on the original Panel 1), was applied to the subject's back and remained there for 48 hours. The results were evaluated after 48 and 72 to 96 hours. Of the 127 subjects, 6 (4.7%) were patch test positive to thiuram mix. See Table 6.

Study No. 2

This study evaluated the efficacy of T.R.U.E. TEST Panel 2.1, which includes four of the Rubber Panel T.R.U.E. TEST allergens (carba mix, black rubber mix, mercaptobenzothiazole, mercapto mix). A total of 121 subjects with suspected contact dermatitis were recruited. T.R.U.E. TEST Panel 2.1, containing 11 allergens and a negative control, was applied to the subject's back and remained there for 48 hours. The results were evaluated after 72 to 96 hours. Of the 121 subjects tested, there were 14 (11.6%) positive patch test reactions to Rubber Panel T.R.U.E. TEST allergens. See Table 6.

Study No. 3

This study evaluated the efficacy of T.R.U.E. TEST Panels 1.1 and 2.1 which includes five of the Rubber Panel T.R.U.E. TEST allergens (carba mix, black rubber mix, mercaptobenzothiazole, mercapto mix and thiuram mix) in a North American patient population referred for patch testing. One hundred nineteen (119) subjects were enrolled. T.R.U.E. TEST Panels 1.1 and 2.1, containing 23 allergens and a negative control, were applied to the subject's back and remained there for 48 hours. The results were evaluated at 72 to 96 hours after application. Among the 119 subjects tested, there were 14 (11.8%) patch test positive reactions to Rubber Panel T.R.U.E. TEST allergens. See Table 6.

Study No. 4

This open-label, multicenter study evaluated the efficacy of T.R.U.E. TEST. All five of the Rubber Panel T.R.U.E. TEST allergens (carba mix, black rubber mix, mercaptobenzothiazole, mercapto mix and thiuram mix) and a negative control were included in this study. Fifty (50) prospectively identified subjects with suspected contact dermatitis were recruited. Of these recruited subjects, the most common

dermatitis site was the hand (21 (42.0%)), and the most common dermatitis type was allergic (34 (68.0%)). T.R.U.E. TEST Panels 1.1 and 2.1 (24 allergens or allergen mixes, no negative control) were applied to the subject's back and remained there for 48 hours. The results were evaluated after 72 to 96, 120, or 168 hours. Of the 50 subjects, there were 8 (16.0%) positive reactions (occurring at 72-96 hours) to the Rubber Panel T.R.U.E. TEST allergens. See Table 6.

Study No. 5

This comparative study evaluated the relationship between reactions caused by a natural sensitizer, such as nickel-containing costume jewelry, and T.R.U.E. TEST. Forty-nine (49) subjects with a history of cutaneous reactions to jewelry were tested with T.R.U.E. TEST Panel 1.1, which included thiuram mix found on the Rubber Panel T.R.U.E. TEST. A medallion containing approximately 20% nickel served as a positive control. Reactions were evaluated 72 to 96 hours after application. There were 2 (4.1%) positive patch test reactions to thiuram mix. See Table 6.

Table 6- Number and Frequency of Positive Reactions to the Rubber Panel T.R.U.E. TEST Allergens 72 to 96 Hours Following T.R.U.E. TEST Patch Application Among Adults 18 Years of Age and Older with Suspected Dermatitis

	Study 1 N ^a = 127 n ^b (%)	Study 2 N ^a =121 n ^b (%)	Study 3 N ^a =119 n ^b (%)	Study 4 N ^a =50 n ^b (%)	Study 5 N ^a =49 n ^b (%)	Combined Studies n ^b /N ^a (%)
Carba Mix	NA ^c	2 (1.7)	3 (2.5)	1 (2.0)	NA ^c	6/290 (2.1)
Black Rubber Mix	NA ^c	2 (1.7)	2 (1.7)	0 (0.0)	NA ^c	4/290 (1.4)
Mercapto Mix	NA ^c	4 (3.31)	2 (1.7)	2 (4.0)	NA ^c	8/290 (2.8)
Thiuram Mix	6 (4.7)	NA ^c	6 (5.0)	4 (8.0)	2 (4.1)	18/345 (5.2)
Mercaptobenzothiazole	NA	6 (5.0)	1 (0.8)	1 (2.0)	NA ^c	8/290 (2.7)

a N= Study Population

b n=Number of subjects with positive reactions to the specific rubber allergen

c NA= Not all 5 rubber allergens were evaluated in all studies

14.2 Children and Adolescents 6 through 17 Years of Age

In an open-label, prospective, single-center study conducted in the U.S., 101 children and adolescents 6 through 17 years of age with suspected allergic contact dermatitis had 3 T.R.U.E. TEST panels (Panel 1.1, 2.1 and 3.1) applied to their back or upper arm for 48 hours (study 6). The T.R.U.E. TEST panels contained 28 allergens of which 5 were rubber allergens/allergen mixes. The frequency of positive reactions to Rubber Panel T.R.U.E. TEST allergens recorded at Day 3-4 and Day 7 after patch application is found in Table 7.

Table 7- Number and Frequency of Positive Patch Test Reactions to Rubber Panel T.R.U.E. TEST Allergens on Day 3-4 and Day 7 Following T.R.U.E. TEST Application Among Children and Adolescents 6 through 17 Years of Age with Suspected Contact Dermatitis (Study 6^a)

Rubber Allergen	N ^b	Day 3-4 n ^c (%)	Day 7 n ^c (%)	Total Positives n ^c (%)
Black Rubber Mix	101	2 (2.0)	0 (0.0)	2 (2.0)
Carba Mix		7 (6.9)	1 (1.0)	7 (6.9)
Mercapto Mix		2 (2.0)	1 (1.0)	2 (2.0)
Mercaptobenzothiazole		2 (2.0)	1 (1.0)	2 (2.0)
Thiuram Mix		6 (5.9)	1 (1.0)	7 (6.9)

^aOpen-label, prospective study conducted in the U.S. (NCT- 00795951)

^bN= Total number of children and adolescents in the pediatric clinical trial

^cn= Number of children with positive patch test reactions to the specified rubber allergen on the specified day

One participant reported an irritant reaction to thiuram mix on Day 3 after patch application. The number (percentage) of participants with doubtful reactions to rubber allergens at Day 3-4 and/or Day 7 following patch application were as follows: carba mix (n=1 (1.0%)), black rubber mix (n=3 (3.0%)), mercapto mix (n=0), mercaptobenzothiazole (n=1 (1.0%)), and thiuram mix (n=6 (5.9%)). No subject reported a positive reaction to the negative control at any time.

16 HOW SUPPLIED/STORAGE AND HANDLING

Multipack carton containing five units. Each unit consists of one adhesive panel containing 6 patches – NDC: 67334-0500-1.

Store Rubber Panel T.R.U.E. TEST between 20°–25° (68°–77 °F). Do not freeze. Failure to store Rubber Panel T.R.U.E. TEST as recommended may result in loss of potency and inaccurate test results.

17 PATIENT COUNSELING INFORMATION

Inform the patient of the following:

- Patients should seek immediate medical attention and contact their healthcare provider if they experience symptoms of a severe allergic reaction such as trouble breathing or wheezing; a swollen tongue or throat; a drop in blood pressure resulting in dizziness or fainting; a weak and rapid pulse; hives or widespread itching [See *Warnings and Precautions (5.1)*].
- Patients may remove the panel themselves if advised by their healthcare provider to do so or if they are experiencing systemic symptoms [See *Warnings and Precautions (5.1)*].
- Itching and burning sensations are common with patch testing and may be severe in extremely sensitive patients.
- Avoid UV exposure and tanning beds [See *Dosage and Administration (2.1)*].
- Patients should report to their physician any reactions at the patch test site occurring seven or more days after panel removal to identify potential late or persistent reactions or possible sensitizations [See *Warnings and Precautions (5.2,5.7,5.8)* and *Dosage and Administration (2.2)*].
- Avoid getting the panel and surrounding area wet [See *Dosage and Administration (2.1)*].
- Patients should avoid physical activity that may result in reduced adhesion or actual loss of the test panel [See *Dosage and Administration (2.1)*].
- Patients should avoid excessive sweating and keep the test panel and surrounding area dry [See *Dosage and Administration (2.1)*].

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