

Pharmacovigilance Plan Review

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Subject: BLA 125579.0

Product: Rubber Panel T.R.U.E. Test

Applicant: SmartPractice Denmark ApS (SPD)

| Proposed Indication: 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.

BLA Submission: 09-JAN-2006

Resubmissions 15-AUG-2006 (following Complete Response)
21-AUG-2014 (following Complete Response)
27-AUG-2015

PVP Submission: 27-AUG-2015

Action Due Date: 26-FEB-2016

1. Introduction

a. Product description

The Rubber Panel T.R.U.E. Test is a set of epicutaneous patch tests used as an aid in the diagnosis of allergic contact dermatitis (ACD) in individuals whose history suggests sensitivity to natural or synthetic rubber. The panel is applied to healthy skin on the back for 48 hours and then removed. The area is evaluated at 48, 72 and 96 hours for reactions consistent with allergic contact dermatitis. Late positive reactions may occur 7-10 days after application of the panel and patients should be advised to report these reactions. Late positive reactions, occurring more than 14 days after application of the panels, may be indicative of active sensitization from application of the panel.

The test includes 5 separate substances or mixtures including chemical additives used to preserve, stabilize and prevent rubber degradation. The panel is based upon knowledge of rubber manufacturing processes together with evaluations in exposed individuals with suspected ACD related to rubber.

Rubber Panel

1. Negative control (uncoated **b) (4)** polyester patch)
2. Carba mix
3. Black rubber mix
4. Mercaptobenzothiazole
5. Mercapto mix
6. Thiuram mix

Test interpretation (International Contact Dermatitis Research Group)

?	Doubtful reaction: faint macular erythema only
+	Weak positive: 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 do not indicate allergy

Note: Itching is a symptom expected to accompany a positive reaction but is not a grading criterion.

Background

Natural and synthetic rubber exposure is estimated to result in sensitization of 5-25% of US workers in at-risk occupations (healthcare, construction, rubber product manufacturing). Reactions to rubber products include immune-mediated sensitization known as allergic contact dermatitis, and irritant contact dermatitis, a cytotoxic rather than immunologic reaction – both can be manifested by skin redness, burning, edema, cracking, itching, and papules. And both can chronically impact quality of life and work for many years, and in the case of healthcare workers, the disruption of an intact skin barrier increases the risk of infection with certain pathogens, e.g., HIV, Hepatitis C.

Children and adults can also be sensitized to natural and synthetic rubber through dental and medical exposures, sports equipment, toys and shoes.

A relevant diagnostic test, such as Rubber Panel T.R.U.E. Test, can be used to diagnose allergic contact dermatitis based upon a positive result and distinguish it from irritant dermatitis which yields a negative result, allowing for earlier and more specific medical interventions as well as avoidance and product substitutions when feasible.

The five rubber-based allergen or allergen mixes described above comprise a total of 14 allergens, and are included together with a blank (b) (4) patch which serves as a negative control. Structurally related allergen mixes have been separated as much as possible on the panel to minimize the potential for cross-reactivity and false positives following application.

The currently approved three-panel T.R.U.E. TEST contains a total of 28 separate allergens or allergen mixes as well as a negative control. The rubber-based components, which are the subject of this submission, are a subset of the approved T.R.U.E. Test components found in positions 15, 16, 22, 24 and 32 of the T.R.U.E. TEST.

b. Pertinent regulatory history

- i. Prior licensure in the US (if a supplement) or other nations
 - 1. summary of indications and usage

c. Major postmarketing safety findings

- i. CBER Complete Response letters
CBER/OVRR has issued 3 Complete Response Letters since the original submission of a BLA for this product in 2007, involving various clinical, manufacturing and regulatory deficiencies. No particular safety issues have been identified in the review of these previous submissions.
- ii. Relevant prior Advisory Committee meetings: None

d. Objective

The purpose of this review is to identify potential safety issues that may require action beyond routine pharmacovigilance.

2. Materials reviewed

a. Pharmacovigilance Plan (Appendix 5)

See Section 3, below.

b. Clinical Overview (Appendix 1)

Reference is made to the five rubber-based allergens or allergen mixes comprising the Rubber Panel T.R.U.E. TEST as being included in the currently licensed three-panel T.R.U.E. Test.

No clinical study safety data are provided.

c. Clinical Study Report: Mekos 07 29P1/2/3 401 (Appendix 2)
See Section 3. a. (below)

d. Postlicensure Safety Data for related products (Appendix 5)

A total of 102 adverse event reports (five classified as serious) have been received in association with the use of various T.R.U.E. TEST panels that have been marketed over the past 20 years.

e. International postmarketing experience with the same product (Appendix 5)
Rubber Panel T.R.U.E. TEST has not been marketed, but its components are included in the currently marketed T.R.U.E. test panels. See item d., immediately above.

3. **Pharmacovigilance Plan Review**

a. Clinical Safety Database

The submitted safety database is limited to a single pediatric study.

Clinical Study Report: Mekos 07 29P1/2/3 401 (Pediatric/Adolescents)

Clinical Evaluation of T.R.U.E. TEST® Panel 1.1, 2.1 and 3.1 in children and Adolescents

NOTE: The allergens proposed to be used in the Rubber Panel T.R.U.E. TEST are a subset of the various allergens contained in the three test panels used in this study.

Overview

- Open-label, single center study
- Healthy pediatric subjects 6-18 years old with suspected ACD
- N = 102 subjects analyzed
- Five clinic visits over 21 days following application of test
- Investigator evaluations including recording patient-reported adverse events
- Efficacy evaluations through 3 weeks (Visit 5)
- Safety monitoring through 3 weeks (Visit 5) with photographic documentation
- Parameters included AEs, SAEs, local reactions including late and/or persistent skin reactions and reactions to the tape used to adhere the panel to the skin for initial 48 hour study period
- Pregnancy testing was conducted in all females 15-18 years of age and in those post onset of menarche

Characterization of enrolled study population

Disposition: 2 discontinuations early (1 lost to follow-up; 1 withdrew consent)

Mean age: 11.6 years

Age groups: 6-8 years (27.5%), 9-12 years (28.4%), 13-18 years (44.1%)

Demographics: 52% females / 48% males; Caucasian 39.2%, Hispanic 31.4%, Asian 12.7%, African American 6.9%

Safety Results

- Adverse events (AEs) were not coded and therefore are presented using the actual descriptions reported by the investigators.
- No deaths
- No serious AEs
- No AEs led to subject discontinuation
- 35 subjects reported fifty-two AEs, 59.6% considered possibly related to panel application
- 50 AEs characterized as mild to moderate in severity
- 2 AEs characterized as severe:
 - Subject 008
Visit 3 (Day 3 or 4)
worsening rash, infected, yellow crusting
considered possibly related to Rubber Panel T.R.U.E. TEST
 - Subject 096
Visit 3 (Day 3 or 4)
worsening rash
considered not related to Rubber Panel T.R.U.E. TEST
Note: also reported to have super infected plaques
- Approximately 80% experienced no or weak tape-induced irritation
- Weak to strong itching or burning was reported upon removal of each of the three T.R.U.E. TEST panels ranged from 39.6% - 66.3%
- 4 subjects experienced 7 persistent reactions: 4 reactions associated with nickel sulfate (1 instance each of mild infiltration and mild pruritus, and 2 instances of mild hyperpigmentation), and 1 reaction each associated with Cl+Me-isothiazolinone (moderate hypopigmentation), quaternium-15 (mild hyperpigmentation), and diazolidinyl urea (mild hyperpigmentation).
- There were no late-onset skin reactions

Previous Safety Experience with the Approved T.R.U.E. TEST (Adults)

The referenced T.R.U.E. TEST US package insert contains pooled data from eight clinical trials; information is not provided separately for individual allergens or for the subset of allergens contained in the Rubber Panel.

Adverse Events from - T.R.U.E. TEST Clinical Studies

Total Subjects	858	100%
Subjects with:		
Erythema	44	5%
Dermatitis flare	1	0.12%
Hyperpigmentation	46	5%
Pruritus	46	5%
Scarring	2	0.23%
Urticaria	1	0.12%
Rash	2	0.23%
Delayed Reaction (allergen known)	1	0.12%
Delayed Reaction (allergen unknown)	4	0.47%
Sensitization (potential)	1	0.12%
Sensitization (probable)	2	0.23%
Infiltration/Skin thinning	5	0.58%
Any adverse event	155	18.07%

Source: BLA 125579.0, Appendix 2, page 232/1095

Adverse Events at Patch Test Removal - T.R.U.E. TEST Clinical Studies

Total Subjects	858	100%	
Those with:			
Itching	Mild	266	31%
	Moderate	40	5%
	Strong	76	9%
Burning	Mild	211	25%
	Moderate	40	5%
	Strong	45	5%
Any adverse event	678	79%	

Source: BLA 125579.0, Appendix 2, page 232/1095

- b. Safety concerns and sponsor's proposed actions**
 - i. Important identified safety issues

Sensitization

Sensitization to an allergen in the Rubber Panel T.R.U.E. Test is irreversible and estimated to occur in 1-1.5% of exposed patients following patch skin testing (Lashapelle 2012). Studies 1-5, which evaluated various allergens including one or more of the Rubber Panel T.R.U.E. TEST allergens in adults, reported a total of 8/466 (0.02%) patients with sensitization (possible) but the specific allergens are not provided. Three

PM reports of sensitization have been reported following use of other T.R.U.E. Test products.

Proposed actions: Product labeling, routine pharmacovigilance

ii. Important potential safety issues

Anaphylactic reaction

Anaphylaxis is a serious, uncommon, but not unexpected reaction after exposure to an allergen in a sensitized individual. Fifteen PM reports of systemic reactions / anaphylaxis have been reported following use of other T.R.U.E. Test products. Anaphylactic / anaphylactoid reactions have been infrequently associated with exposure to neomycin or bacitracin in patch testing (Lashapelle 2012).

Proposed action: Routine pharmacovigilance

OBE/DE Reviewer comment: Anaphylaxis is appropriately addressed in the submitted Package Insert in the Contraindications section, and in the Warnings and Precautions section.

iii. Important missing information

Use of Rubber Panel T.R.U.E. Test in pregnant/nursing women

Proposed action: Routine pharmacovigilance

c. Sponsor's proposed future actions and timelines

i. Enhanced pharmacovigilance activities proposed by sponsor: None

ii. Review of Postmarketing Study proposal or protocol synopsis: N/A

4. **Postlicensure Safety Review**

Rubber Panel T.R.U.E. TEST has not been marketed as of the date of this review.

T.R.U.E. TEST is a US-licensed product consisting of a panel of 35 epicutaneous allergen and allergen mix patches including the 6 patches proposed to be included in the Rubber Panel T.R.U.E. TEST.

The most recent periodic adverse event report for T.R.U.E. TEST for the reporting period from December 1, 2013, through November 30, 2014 indicates that a total of (b) (4) tests were reported sold in the US and a total of 14 adverse events reports were received by the manufacturer. The manufacturer notes an increase in reports of strong and long-lasting positive reactions for gold sodium thiosulfate allergen, which was added to the

T.R.U.E. TEST in 2012. This allergen is not included in the Rubber Panel T.R.U.E. TEST.

5. **Integrated Risk Assessment**

No safety issues have been identified by this reviewer from any source that would trigger a safety postmarketing study as a postmarketing commitment (PMC) a postmarketing requirement (PMR) or a Risk Evaluation and Mitigation Strategy (REMS).

6. **Recommendations**

a. Routine pharmacovigilance

b. There does not appear to be a need for a REMS or a PMR postmarketing safety study or enhanced pharmacovigilance based upon review of this submission.

c. Appendix 4a, annotated package insert, Page 5/26, line 282, describing Table 2 should be corrected to indicate the table summarizes five clinical studies rather than ten clinical studies.

References

Lachapelle J.N. and Maiback H. I. Patch testing and Prick Testing – A Practical Guide – Official Publication of the ICDRG (International Contact Dermatitis Research Group). Third edition. 2012.