SUMMARY OF NEVISENSE LABELING INFORMATION

About Nevisense

Nevisense measures electrical impedance of skin lesions and provides an output called the electrical impedance spectroscopy (EIS) score. Electrical impedance is a measure of a material's overall resistance to the flow of alternating electric currents of various frequencies. The principle is that electrical impedance is different in normal versus abnormal tissue.

Indication for Use

Nevisense is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Nevisense should not be used on clinically obvious melanoma. The Nevisense result is one element of the overall clinical assessment. The output of Nevisense should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.

Nevisense is indicated only for use on:

- primary skin lesions with a diameter between 2 mm and 20 mm;
- lesions that are accessible by the Nevisense probe;
- lesions where the skin is intact (i.e. non-ulcerated or non-bleeding lesions);
- lesions that do not contain a scar or fibrosis consistent with previous trauma;
- lesions not located in areas of psoriasis, eczema, acute sunburn or similar skin conditions;
- lesions not in hair-covered areas;
- lesions which do not contain foreign matter;
- lesions not on special anatomic sites (i.e. not for use on acral skin, genitalia, eyes, mucosal areas).

Contraindications

There are no known contraindications.

Warnings and Precautions

Key warnings and precautions for Nevisense use are listed below.

Warnings

- Do not use Nevisense as a screening device. A Nevisense negative reading does not eliminate the possibility that the lesion might be or evolve into a melanoma, see *Pivotal Studies* on page 2. The result should always be considered by the physician in conjunction with other clinical parameters.
- Do not use on lesions already determined to require biopsy based on clinical evaluation. This device is an adjunct tool for evaluation of lesions prior to the decision to biopsy. There is a potential for Nevisense to classify a melanoma as EIS negative and to miss a melanoma. In the

pivotal study results, 4.1% of melanomas (11) pathologically confirmed were classified by Nevisense as negative. In a reader study included in the PMA approval, readers without Nevisense missed 22.8% of melanomas, readers with Nevisense as an adjunct missed 16.4% of melanomas, and 3.3% of melanomas were classified as negative by Nevisense.

- Do not apply excessive pressure when measuring close to a pacemaker in order not to damage the pacemaker
- If a lesion bleeds, appears ulcerated, or if the skin appears compromised after measurement, change the electrode before conducting additional measurements. This is in order to minimize the risk of transferring possible malignant cells.
- Nevisense safety and effectiveness has not been established in patients age 30 and below. In the pivotal study, there were 296 total lesions in patients 18-30 years old with few (7 lesions, 2.6%) melanomas. The Nevisense sensitivity was 57.1% and specificity was 38.4% for melanomas in patients 18-30 years old compared to patients 31 years and older where the sensitivity was 97.7% and specificity was 29.9%.

Precautions

- Nevisense safety and effectiveness has not been established in patients with Fitzpatrick Skin Type 5 and 6.
- Nevisense may only be used by dermatologists who have successfully completed the Nevisense training.

Potential Adverse Effects

Potential adverse effects of any skin examination for melanoma may include: false negative results, which may lead to delays in diagnosis and treatment of melanoma, potentially increasing morbidity and mortality; and false positive results, which may result in unnecessary medical intervention including more frequent screening and invasive skin biopsy procedures.

Pivotal Study Results

Clinical Endpoints

Safety was evaluated by the occurrence and incidence of all adverse events (AEs) reported for study subjects throughout their participation in the study. The primary safety endpoint was the absence of serious device-related events.

The primary effectiveness endpoint of the study consisted of two co-endpoints aiming to show sensitivity ≥ 0.90 to detect malignant melanoma, and non-randomness. For the primary co-endpoints, a lesion is considered positive according to histology only in cases of malignant melanoma.

The secondary effectiveness endpoints included the same co-endpoints for sensitivity and non-randomness as the primary endpoint; however, for the secondary endpoint, a lesion was considered positive by histology in cases of melanoma, carcinomas (including SCC, BCC, Merkel Cell Carcinoma, and actinic keratosis), and Severe Dysplastic Nevi. The secondary effectiveness endpoints were pre-specified in the pivotal study protocol.

Safety Results:
28 subjects (1.5% of all subjects) experienced a total of 36 adverse events. No serious adverse event, serious adverse device effect or unanticipated adverse device effect was observed throughout the study. Most AEs were of mild severity (33 of 36). The one severe event (migraine headache) was considered unrelated to the device. Two events of moderate severity (both for wound infection following excision) were considered unlikely to have been related to the device. 12 subjects (0.6% of all subjects) experienced 14 events that were considered by investigators to be possibly, probably, or definitely related to the device. These events involved bleeding during measurement (n=6); itching (n=1) at the measurement site; pain, soreness, or bruising (n=3) or slight tingling sensation (n=2) at the measurement site; and headache (n=2).

Effectiveness Results:
Primary Effectiveness Analysis (on Primary Effectiveness Population, using Primary Reference Diagnosis (positive = melanoma only))
Co-Primary endpoint 1: Sensitivity of Nevisense for Detecting Melanoma
For the primary effectiveness analysis, in accordance with the primary endpoint definition, disease positive means lesions declared by the histology as melanoma (positive = melanoma only). In the primary effectiveness population, 267 or 13.7% of lesions were by histology, diagnosed as melanoma. The Nevisense device correctly identified 256 melanoma lesions out of 267 melanoma lesions, yielding sensitivity of 95.9%. Of 1,684 lesions that were not melanoma, 527 were diagnosed Negative by Nevisense, yielding specificity of 31.3%.
Co-Primary Endpoint 2: Sensitivity + Specificity > 1 for Melanoma Detection by Nevisense
This endpoint assessed whether the Nevisense is better at detecting melanoma than randomly flipping a coin to decide whether lesions contain Melanoma. In order to statistically assess this, the odds ratio from statistical logistic regression modelling was used. An odds ratio statistically greater than 1 from this model means that the sum of sensitivity and specificity is also statistically greater than 1. The results are given in the following table. The odds ratio is 10.5 ($P < 0.0001$), meaning that odds ratio is statistically greater than 1, which means that sum of sensitivity and specificity is statistically greater than 1.

Table: Results from mixed logistic model for co-primary endpoint 2

Odds Ratio			
Estimate	Two-Sided 95% Lower CL	Two-Sided 95% Upper CL	P-Value
10.5	5.6	19.5	<.0001

Secondary Effectiveness Analysis (on Secondary Effectiveness Population, using Secondary Reference Diagnosis (positive = melanoma, carcinomas, or severe dysplastic nevi))
The secondary effectiveness endpoints included the same co-endpoints for sensitivity and non-randomness as the primary endpoint; however, for the secondary endpoint, a lesion was considered positive (according to histology) in cases of melanoma, carcinomas (including SCC, BCC, Merkel Cell Carcinoma, and actinic keratosis), and Severe Dysplastic Nevi. Other than the change in definition of positive lesions, the statistical approach for the secondary effectiveness endpoints is the same as the primary effectiveness endpoints. . In the secondary effectiveness analysis, 26.0% of lesions are positive by histology. The Nevisense device correctly identified 472

Positive lesions of the 510 in the sample, yielding a sensitivity of 92.5%. Of 1451 Negative lesions, 500 were diagnosed Negative by Nevisense, yielding specificity of 34.5%.
Co-Secondary Endpoint 2 (non-randomness): The odds ratio is 6.4, significantly greater than 1 (P < 0.0001), indicating, as in the primary effectiveness analysis, that the Nevisense outcome is not random.

Table: Results from mixed logistic model for co-secondary endpoint 2

Odds Ratio			
Estimate	Two-Sided 95% Lower CL	Two-Sided 95% Upper CL	P-Value
6.4	4.5	9.2	<.0001

Exploratory Effectiveness Analyses
The following additional analysis of the primary co-endpoints was conducted in analysis populations not prospectively defined in the Statistical Analysis Plan (SAP).
Primary Effectiveness Endpoints (with Updated Primary Effectiveness Analysis Population)
The primary effectiveness endpoints analyses were repeated on an Updated Primary Effectiveness analysis population, which excluded eight additional lesions due to an invalid measurement procedure (measurements completely outside the border of the lesion on healthy skin), a major protocol deviation, which was discovered after database lock. In this population, which reflects device accuracy for lesions assessed according to device instructions for use:

- Melanoma sensitivity was 96.6% with lower one-sided 95% confidence limit of 94.2%.
- The outcome of Nevisense device remained highly related to the reference outcome (P<0.0001), i.e. non-random. The obtained odds ratio of the device versus reference was 12.9, with a two-sided 95% confidence interval of 6.5 to 25.4.

Therefore, both co-primary hypotheses of this study were also met for the updated primary effectiveness population.An additional analysis investigating the dependency between accuracy and lesion type was performed using the Updated Primary Effectiveness Analysis population. This analysis excluded the 8 lesions previously mentioned and used for Reference Diagnosis the definition of the secondary confirmatory endpoint. Table below presents sensitivity and specificity for different lesion types. As can be seen from this table, the overall sensitivity for melanoma is 96.6%. The sensitivity for high stage melanoma (thickness T2, T3 and T4) is 100%, and sensitivity for melanoma with thickness T1 is above 98%. Sensitivity for in-situ is, as expected, lowest at 93.8%. Overall specificity is 34.4%, which includes mild to moderate nevi, melanocytic nevi, and other lesions. In this analysis, severe dysplastic nevi, carcinomas, and actinic keratosis are counted as positives. Carcinomas are malignant lesions and are therefore presented as positive. Severe dysplastic nevi are presented in a separate category because they can be considered positive or negative, depending on the clinical conventions adopted in different countries. This analysis was done to help communicate the numbers for lesion subcategories to the clinical community.

Updated Primary Effectiveness Analysis Population: Sensitivity and Specificity by Lesion Type

Sensitivity and Specificity Analyses (Assuming Independency)										
Reference Diagnosis (Secondary)	Sensitivity	Specificity	TP	FN	TN	FP	Total N	95% Two-sided LCL	95% Two-sided UCL	95% One-sided LCL
Melanoma (Total)	**96.6**		**256**	**9**			**265**	**93.65**	**98.44**	**94.15**
Melanoma: Tis (In-situ) (= 0mm)	93.8		105	7			112	87.55	97.45	88.58
Melanoma: T1 (0-1 mm)	98.2		111	2			113	93.75	99.78	94.53
Melanoma: T2 (1-2 mm)	100		35	0			35	90	100	91.8
Melanoma: T3 (2-4 mm)	100		4	0			4	39.76	100	47.29
Melanoma: T4 (> 4mm)	100		1	0			1	2.5	100	5
Severe Dysplastic Nevus	**84.1**		**132**	**25**			**157**	**77.4**	**89.42**	**78.48**
Non-MM (BCC+SCC+AK)	**98.4**		**62**	**1**			**63**	**91.47**	**99.96**	**92.69**
Non-MM Excluding AK	100		55	0			55	93.5	100	94.7
BCC	100		48	0			48	92.6	100	93.9
SCC	100		7	0			7	59.0	100	93.5
AK*	87.5		7	1			8	47.3	99.7	52.9
Merkel Cell Carcinoma	**100**		**1**	**0**			**1**	**100**	**N/A**	**N/A**
Mild to Moderate Dysplastic Nevus		**36,1**			**357**	**631**	**988**	**33,13**	**39,22**	**33.6**
Melanocytic Nevus		**36,7**			**131**	**226**	**357**	**31,68**	**41,93**	**32.45**
Other		**11,6**			**13**	**99**	**112**	**6,33**	**19,03**	**7.0**
Overall Specificity		**34,4**			**501**	**956**	**1457**	**31,95**	**36,89**	**32.33**

TP: True Positive, FN: False Negative, TN: True Negative, FP: False Positive, LCL: Lower Confidence Limit, UCL:Upper Confidence Limit

* AK (actinic keratosis) is a precursor lesion to SCC (Squamous Cell Carcinoma), and not an SCC per se.