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October 4, 2019

Division of Dockets Management
Department of Health and Human Services,
Room 1061(HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Subject: ANDA Suitability Petition for Solifenacin Succinate, 5 mg and 10 mg, Orally Disintegrating Tablets

Dear Sir or Madam,

As the US Agent for Intas Third Party Sales 2005, S.L., located at Moll de Barcelona s/n, World Trade Center, Edifici Est, 6th Fllor, 08039, Barcelona, Spain (named as INTAS from hereafter), I am submitting an ANDA Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act), and in accordance with 21 CFR (Code of Federal Regulation) § 10.30 and 314.93.

This Suitability Petition, for which appropriate data is presented in the enclosed document from INTAS, requests that the FDA determine that Solifenacin Succinate developed by INTAS, as 5 mg and 10 mg orally disintegrating tablets (ODT), is suitable for submission in an Abbreviated New Drug Application (ANDA). The Reference Listed Drug (RLD) is Vesicare® 5 mg and 10 mg film-coated tablets from Astellas Pharma US Inc. (NDA #021518).

Please do not hesitate to contact me by phone at 802-865-0261 or email bthompson@Reguliance.com to address any questions or concerns regarding this suitability petition.

Sincerely,

Bruce Thompson
REGULIANCE LLC
28 Hungerford Terrace
Burlington, Vermont USA 05401
802.865.0261

Barcelona, 30th September 2019

ANDA Suitability Petition for
Solifenacin INTAS orally disintegrating tablets
(5 mg and 10 mg)

A. Action Requested:

The Suitability Petition requests that the FDA determine and declare that Solifenacin Succinate, 5 mg and 10 mg, Orally Disintegrating Tablets (ODT) is suitable for submission in an Abbreviated New Drug Application (ANDA). This Suitability Petition pursuant to Section 505(j)(2)(C) of the FDC Act and 21C.F.R. §314.93, is the appropriate mechanism for securing FDA authorization to submit an ANDA for a drug product that differs in dosage form from the Reference Listed Drug (RLD).

The Reference Listed Drug (RLD) upon which this petition is based is Vesicare® film-coated tablets from Astellas Pharma US Inc., which FDA approved prior on Nov 19, 2004 under NDA #021518, and is marketed in 5 mg and 10 mg strengths as identified in the Orange Book. The relevant copy of the pages from the current Electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for Vesicare® is provided as ***Attachment 1***.

Approval of this Suitability Petition would allow INTAS to submit Solifenacin Succinate, 5 mg and 10 mg, ODT as an ANDA.

B. Statement of Grounds:

The FDC Act Section 505(j)(2)(C)(iii) and 21C.F.R. §314.93, provides for the submission of an Abbreviated New Drug Application for a drug product that has a different dosage form from the RLD product provided that the FDA has approved a suitability petition proposing such an application.

Vesicare®, the RLD for the proposed drug product, containing either 5 mg, or 10 mg of Solifenacin Succinate, as film-coated immediate-release tablets, is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency. A copy of the most recent labeling for Vesicare® (Revised April 2019) is provided as ***Attachment 2***.

INTAS proposes an alternative immediate-release oral tablet dosage form, bioequivalent to Vesicare®, in the exact same dosage strengths (5 mg and 10 mg). Table 1 presents the comparison between approved marketed and proposed drug product.

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Table 1 - Comparison of Approved Drug Product to Proposed Drug Product

Product Name	**RLD – Vesicare®**	**Solifenacin INTAS orally disintegrating tablets**
Drug Substance	Solifenacin Succinate	
Dosage Strengths	5 mg and 10 mg	
Dosage Form	Film-coated tablets	Orally disintegrating tablets
Route of Administration	Oral	
Indication	It is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency	
Method of administration (Dosing Information)	VESIcare should be taken with water and swallowed whole. It can be administered with or without food.	Solifenacin INTAS orally disintegrating tablets should be taken orally and should be sucked until completely disintegrated, and then swallowed. It can be administered with or without food.
Dosing regimen	The recommended dose is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.	
Dosage adjustments	For patients with severe renal impairment (CLcr < 30 mL/min), a daily dose greater than 5 mg is not recommended. For patients with moderate hepatic impairment (Child-Pugh B), a daily dose greater than 5 mg is not recommended. Use in patients with severe hepatic impairment (Child-Pugh C) is not recommended When administered with potent CYP3A4 inhibitors such as ketoconazole, a daily dose greater than 5 mg is not recommended.	
Composition in inactive ingredients (in addition to the active ingredient Solifenacin succinate)	Each dosage unit contains the following inert ingredients: - lactose monohydrate - hypromellose 2910 - corn starch - magnesium stearate - talc - polyethylene glycol 8000 - titanium dioxide - yellow ferric oxide (Vesicare® 5 mg) - red ferric oxide (Vesicare® mg)	Each dosage unit contains the following inert ingredients*: - lactose monohydrate - hypromellose - polacrilin potassium - mannitol - sucralose - croscarmellose sodium - sodium stearyl fumarate - peppermint flavor - menthol aroma/flavor

It is confirmed that all the inactive ingredients of Solifenacin INTAS orally disintegrating tablets, in both dosage strengths (5 mg and 10 mg), remain below the applicable IID's Maximum potency per dose, which are outlined

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hereafter, and therefore the concerned composition differences in relation to the RLD do not raise any safety concern:

- *Lactose monohydrate: 126.1 mg (UNII: EWQ57Q8I5X); ORAL; TABLET, CHEWABLE (this limit is regarded as acceptable for the concerned dosage form and route of administration)*
- *Hypromellose: 18 mg (UNII: 3NXW29V3WO); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Polacrilin potassium: 40 mg (UNII: 0BZ5A00FQU); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Mannitol: 971.36 mg (UNII: 3OWL53L36A); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Sucralose: 12 mg (UNII: 96K6UQ3ZD4); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Croscarmellose sodium: 48 mg (UNII: M28OL1HH48); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Sodium stearyl fumarate: 29 mg (UNII: 7CV7WJK4UI); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Peppermint flavor: 3.5 mg (UNII: -); ORAL; TABLET, ORALLY DISINTEGRATING*
- *Menthol aroma/flavor: 7 mg (UNII: -); ORAL; TABLET, ORALLY DISINTEGRATING*

The proposed labeling for Solifenacin INTAS orally disintegrating tablets is provided as ***Attachment 3***. As it can be seen in the side-by-side comparison of Vesicare® and Solifenacin INTAS orally disintegrating tablets labeling provided as ***Attachment 4***, the only differences between the two products' labeling are those related to the method of administration, formulation-specific data, company name and product description.

The concerned orally disintegrating tablets formulation of Solifenacin succinate has been developed by INTAS to obtain an alternative immediate-release oral dosage form bioequivalent to Vesicare® that enhances and promotes therapeutic convenience, adherence and compliance:

- ODT do not require water or other liquids, so the developed product can be taken in situations where patients do not have access to water whatsoever contributing to treatment adherence.
- ODT serve as preferred dosage form for patients suffering from difficulty in swallowing, e.g. drug-induced esophagitis, elderly people or patients with impaired swallowing function.
- Additionally, it is worthy to note that many patients suffering from incontinence and/or increased urinary frequency also suffer of nocturia. Nocturia medication is given at night, mainly in form of fast disintegrating tablets and should be taken in absence of fluid intake.

In this sense, the formulation was designed in order to disintegrate in the mouth in less than 1 minute and with an ion-exchange resin (Polacrilin potassium) that complexes the drug substance at buccal pH, avoiding local absorption. Thus, after disintegration of the tablet, the drug substance is not absorbed and remains adsorbed within a drug substance:resin complex. When the drug substance:resin complex reaches the acidic pH conditions of the stomach, the ion-exchange resin releases the drug substance. Therefore, the initial disintegration of the tablet is buccal, but drug dissolution is only expected to initiate in the stomach, similarly to the RLD formulation.

Considering the formulation release properties and the desired bioequivalence to the RLD formulation, the bioavailability of the 10 mg dosage strength of Solifenacin INTAS orally disintegrating tablets shall be studied against the US 10 mg dosage strength of Vesicare® film-coated tablets as this is specified as the reference standard (RS) against which in vivo bioequivalence must be established. Thus, within the scope of the proposed ANDA approach, the developed drug product Solifenacin INTAS orally disintegrating tablets shall demonstrate bioequivalence (90% CI) against the RS in the two bioavailability studies (fasting and fed conditions)

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required by the Office of Generic Drug (OGD) Product-Specific Guidance for Generic Drug Development for bioequivalence studies of Solifenacin Succinate tablets, as provided in ***Attachment 5***. INTAS will therefore support the intended ANDA with full data from the two required bioavailability studies (i.e. full bioequivalence reports in both fasting and fed conditions) successfully establishing the bioequivalence (90% CI) between the 10 mg dosage strength of Solifenacin INTAS orally disintegrating tablets and the US 10 mg dosage strength of Vesicare® film-coated tablets (i.e. the RS).

To characterize the dissolution profile of the product developed by INTAS, comparative dissolution profiles studies with the 10 mg dosage strength of Solifenacin INTAS orally disintegrating tablets studied against the US 10 mg dosage strength of Vesicare® film-coated tablets were performed. It is highlighted that no current USP/NF monograph is available for the drug substance Solifenacin Succinate or for drug products containing Solifenacin Succinate. The following conditions are defined at OGD's Dissolution Methods Database (http://www.fda.gov/cder/ogd/index.htm) for Solifenacin Succinate tablets, as provided in ***Attachment 6***:

Table 2 – OGD's Dissolution Methods Database for Solifenacin Succinate tablets.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Solifenacin Succinate	Tablet	II (Paddle)	50	Water	900	10, 15, 30 and 45	02/19/2008

The above tabulated study conditions (**Table 2**) were therefore considered for the dissolution profile comparisons. Nevertheless, considering that these specific conditions have been defined for comparison of products with the exact same dosage form and Solifenacin INTAS and Vesicare® present different dosage forms, the comparative dissolution profile studies were carried not only in water, but also at pH 1.2, 4.5, 6.8. The obtained results and relevant general discussion/conclusions are provided as ***Attachment 7.*** The consistent differences observed at both dosage strengths (5 mg and 10 mg) between Solifenacin succinate (INTAS) ODT and Vesicare® were expected and are due to the presence of the ion-exchange resin that is incorporated in the oral dispersible formulation to complex the drug substance in non-acidic conditions and avoid buccal dissolution and absorption of the drug substance. Thus, the concerned differences are intentional and are formulation-related, since the formulation has been designed to release the drug substance for dissolution in the stomach acidic conditions, in order to simulate what is expected to happen with the RLD film-coated tablets. If INTAS ODT formulation would not show the concerned behavior in non-acid dissolution conditions, drug substance release, dissolution and absorption would be most likely initiated in the buccal cavity impacting the likelihood of getting a drug substance plasmatic bioavailability similar (90% CI) to the RS.

It is highlighted that the 5 mg and 10 mg dosage strengths of Solifenacin INTAS orally disintegrating tablets are manufactured by the exact same manufacturer and manufacturing process and are quantitatively proportional. Dissolution profile results from ***Attachment 7*** show that both dosage

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strengths of Solifenacin INTAS orally disintegrating tablets have comparable dissolution profiles when tested in pH 1.2, 4.5, 6.8 and water.

Based on the above considerations and established in-vivo bioequivalence, it is INTAS understanding that Solifenacin INTAS orally disintegrating tablets (5 mg and 10 mg) do not present any new safety and/or effectiveness issues with regards to the RLD respective dosage strengths (5 mg and 10 mg), and therefore the appropriate market application for Solifenacin INTAS orally disintegrating tablets (5 mg and 10 mg) is an ANDA. As consequence, INTAS requests that the FDA find and declare that the proposed Solifenacin INTAS orally disintegrating tablets (5 mg and 10 mg) drug product is suitable for submission in an ANDA.

C. Pediatric Use Information

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. As a new dosage form, the orally dispersible tablets are subject to the provisions of PREA.

As previously stated, the developed product Solifenacin INTAS orally disintegrating tablets (5 mg and 10 mg) is proposed to have the exact same indication of Vesicare® film-coated tablets (5 mg and 10 mg), which is indicated for the treatment of overactive bladder (please refer to **Table 1** and **Attachments 2**, **3** and **4**).

The indication for overactive bladder appears on the PREA "List of diseases for which FDA automatically grants a full waiver of pediatric studies" (see ***Attachment 8***), and therefore the requirement, to assessment the safety and effectiveness of the product for the claimed indication in pediatric patients, is automatically waived.

Therefore, the petitioner's request for the Commissioner to find that a change in dosage form from the RLD to INTAS' Orally Dispersible Tablets, with no change in route of administration, should raise no questions with regard to safety or efficacy and the FDA should approve this Suitability Petition.

D. Environmental Impact:

INTAS claims a categorical exclusion under 21 CFR § 25.31.

E. Economic Impact Statement:

INTAS does not believe that this requirement is applicable at this time, but will agree to submit economic impact information, in accordance with 21 CFR § 10.30(b), if requested by the Commissioner following review of this petition.

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F. Certification:

INTAS certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner, which are unfavorable to the Petition.

Enclosures:

- **Attachment 1:** *Copy of the pages from the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for Vesicare®.*
- **Attachment 2:** *Copy of Vesicare® approved labelling (Revised April 2019).*
- **Attachment 3:** *Proposed labeling for Solifenacin INTAS orally disintegrating tablets (5 mg and 10 mg).*
- **Attachment 4:** *Side-by-side comparison of Vesicare® and Solifenacin INTAS orally disintegrating tablets labeling.*
- **Attachment 5:** *Office of Generic Drug (OGD) Product-Specific Guidance for Generic Drug Development of Solifenacin Succinate tables.*
- **Attachment 6:** *Office of Generic Drug (OGD) recommended dissolution method for Solifenacin Succinate tables (Dissolution Methods Database – OGD).*
- **Attachment 7:** *Summary of comparative dissolution profiles studies at pH 1.2, 4.5, 6.8 with the 5 and 10 mg dosage strengths of Solifenacin INTAS orally disintegrating tablets studied against the US 5 and 10 mg dosage strengths of Vesicare® film-coated tablets.*
- **Attachment 8:** *List of diseases for which FDA automatically grants a full waiver of pediatric studies (August 14, 2019 update).*

Sincerely,

Marc Comas Gisbert
Legal Representative
Intas Third Party Sales 2005, S.L.

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