1. GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED

Product name:	Dronabinol + Acetazolamide Unigel (IHL-42X [a])
Type of product (OTC, RX, nutraceutical, cosmetic, other?)	Rx
Brand name / Generic name	Dronabinol 2.5 mg + Acetazolamide 125 mg Unigel Dronabinol 5 mg + Acetazolamide 250 mg Unigel
API(s)	Dronabinol Acetazolamide
Strength(s)	Dronabinol 2.5 mg and Acetazolamide 125 mg Dronabinol 5 mg and Acetazolamide 250 mg
Dosage form	Unigel (Acetazolamide coated tablet immersed in a Dronabinol-solution-filled soft gelatin capsule)
Route of administration	Oral
Dose(s)	To be selected during clinical trials [b]
Physical characteristics (Color, size, shape, text printed, etc.)	Soft gelatin capsule: Opaque, oblong [c] Coated tablet: White, spherical
Type of packaging material	Blister packs [d]
Commercial presentations	Blister packs x 28 capsules [d]
Expiration time required	24 months [b]

Observations:

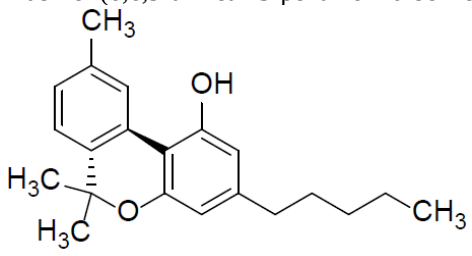
a. Client: Incannex Healthcare Limited
b. See Annex 1 IHL-42X formulation brief August 2021
c. The definitive color of the capsules will be defined once the product development and the clinical trials are finished.
d. See Statement of Work (SOW).

Dronabinol + Acetazolamide Unigel will be developed to seek approval of an NDA in the US.

2. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) (Dronabinol)

Common name:	Dronabinol
CAS number:	1972-08-3 [1]
Description:	Dronabinol: Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol in sesame oil: Clear, colored oil. [2]
Solubility:	Soluble in ethyl acetate, methyl tert-butyl ether (MTBE), acetone, ethanol. Insoluble in water. [2]
Melting point:	200 °C [2]
Polymorphs:	Not applicable. Dronabinol is an oily substance at room temperature. [2]

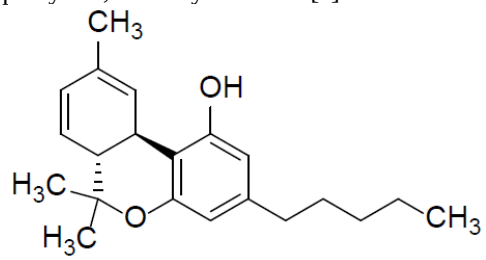
2. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) (Dronabinol)

Stability (Solid state/solution, general information):	Dronabinol in sesame oil is| stable when stored at 2 – 8 °C under protective gas (argon). Dronabinol should be preserved in tight, light-resistant glass containers. [2]
Scheme of degradation route	See impurities for a detailed explanation of the source mechanism of each impurity.
Stability indicators	Acid hydrolysis resulted in 1.95% degradation and the dronabinol peak was found to be 97.14%. Six peaks with a norm% of ≥ 0.10% were detected. Peaks were identified as impurity B (0.33%), impurity G (0.47%), impurity E (1.18%), and impurity H (0.12%) and two peaks (RT 20.4 minutes = 0.12% and 24.7 minutes = 0.49%) were not identified. Base hydrolysis resulted in 1.29% degradation and a 97.80% recovery of the dronabinol peak. Eight peaks were observed to be ≥ 0.10%. Three peaks were identified as impurity G (0.12%), impurity E (0.58%), and impurity H (0.12%). Five peaks were not identified RT 17.6 minutes (0.10%), RT 43.3 minutes (0.56%), RT 43.8 minutes (0.11%), RT 44.5 minutes (0.17%), and RT 45.9 minutes (0.14%). Oxidative stress conditions resulted in 0.33% degradation and 98.76% recovery of the dronabinol peak. One unidentified peak was detected at ≥ 0.10% (RT 21.6 minutes, 0.16%). Photo degradation conditions resulted in 0.65% degradation and 98.44% recovery of the dronabinol peak. Six peaks were detected at ≥ 0.10%. Two peaks were identified as impurity E (0.66%) and impurity H (0.10%). Four peaks were not identified: RT 22.5 minutes (0.23%), RT 22.9 minutes (0.12%), RT 25.2 minutes (0.19%), and RT 38.2 minutes (0.25%). Thermal degradation conditions resulted in 0.85% degradation and 98.24% recovery of the dronabinol peak. Five peaks were detected at ≥ 0.10%. Two peaks were identified as impurity E (0.68%) and impurity H (0.17%). Three peaks were not identified: RT 22.5 minutes (0.32%), RT 23.0 minutes (0.10%), and RT 25.3 minutes (0.13%). Dronabinol in sesame oil was found to be most stable under oxidative stress, photodegradation, and thermal degradation. The drug structure was found to be least stable under acidy hydrolysis and base hydrolysis. [2]
Impurities (Synthetic origin, degradation products and/or metabolites)	Impurity: Cannabinol (6,6,9-trimetil-3-pentil-6H-dibenzopiran-1-ol)  Chemical formula: $C_{12}H_{26}O_2$ Molecular mass: 310.19 g/mol Type of impurity: Process and degradation impurity

2. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) (Dronabinol)

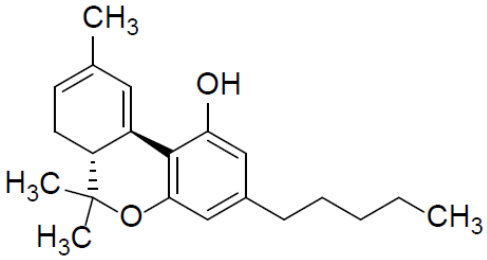
Source mechanism: Cannabinol is an oxidative degradant of D9-THC. [2]

Impurity: DHC Dihydrocannabinol Isomer I ((6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,10a-dihydrobenzo [c]chromen-1-ol)



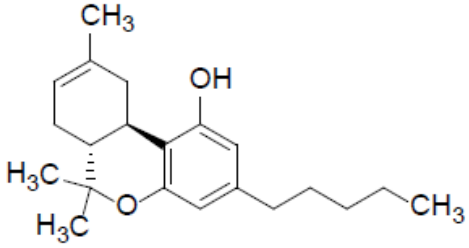
Chemical formula: $C_{21}H_{28}O_2$
Molecular mass: 312.2089 g/mol
Type of impurity: Process and degradation impurity
Source mechanism: DHC Dihydrocannabinol Isomer I is an oxidative degradant of D9-THC. [2]

Impurity: DHC Dihydrocannabinol Isomer II ((3R,4E)-2,2,3-trimethyl-4-[(Z)-2-methylbut-2-enylidene]-7-pentyl-chroman-5-ol)



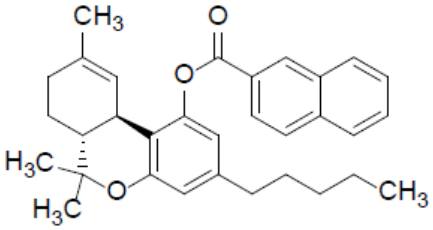
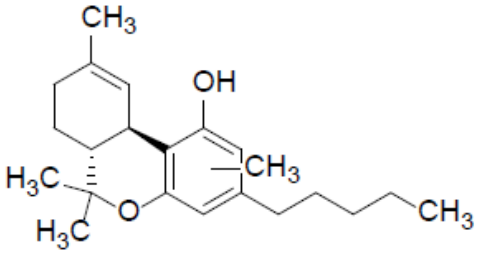
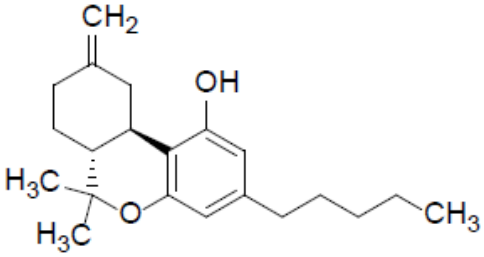
Chemical formula: $C_{21}H_{28}O_2$
Molecular mass: 312.21 g/mol
Type of impurity: Process and degradation impurity
Source mechanism: DHC Dihydrocannabinol Isomer I is an oxidative degradant of D9-THC. [2]

Impurity: D8-Tetrahydrocannabinol (D8-THC) (6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol)

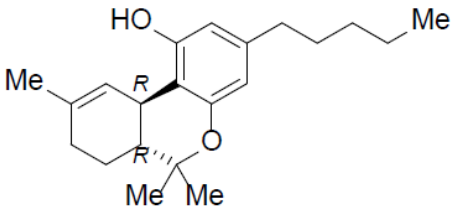


Chemical formula: $C_{21}H_{30}O_2$
Molecular mass: 314.22 g/mol
Type of impurity: Process impurity
Source mechanism: D8-THC is an intermediate in the dronabinol manufacturing route. [2]

2. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) (Dronabinol)

	Impurity: D9-THC-Naphthoylester (Naphthoylene-2-carboxylic acid-(6aR,10aS)-6,6,9-trimethyl-3-pentyl-(6ar,10at)-6a,7,8,10a-tetrahydro-6H-benzo[c]-chromen-1-yl ester)  Chemical formula: $C_{32}H_{36}O_3$ Molecular mass: 468.2664 g/mol Type of impurity: Process impurity Source mechanism: D9-THC-napthoylester is an intermediate in the dronabinol manufacturing route. [2] Impurity: D9-THC-Methylanalogue ((Z)-3-methylpent-2-ene;(3R)-2,2,3,8-tetramethyl-7-pentyl-chroman-5-ol)  Chemical formula: $C_{21}H_{30}O_2$ Molecular mass: 314.22 g/mol Type of impurity: Process impurity Source mechanism: D9-THC-Methylanaloque impurity is derived from an impurity contained in the starting material Olivetol. [2] Impurity: *Exo*-THC ((6aR,10aR)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-1-ol)  Chemical formula: $C_{21}H_{30}O_2$ Molecular mass: 314.2246 g/mol Type of impurity: Process impurity Source mechanism: *Exo*-THC is derived from *exo*-THC naphthoylester, which is an impurity contained in D9-THC-napthoylester and is obtained via saponification of *exo*-THC-naphthoylester. [2]
Biopharmaceutical classification (Biopharmaceutical classification system)	Class II (Low solubility, high permeability) [3]

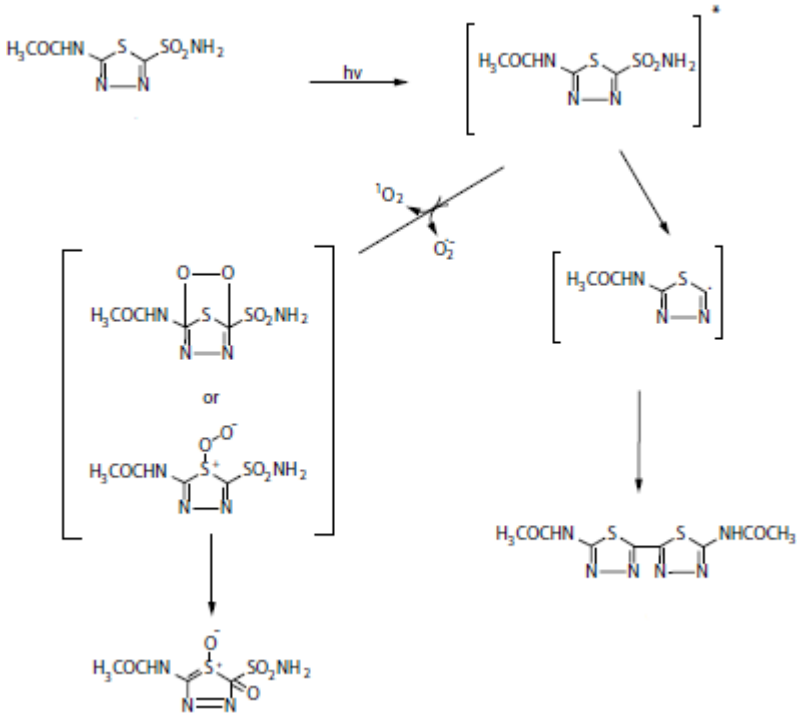
2. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) (Dronabinol)

Toxicological classification (Contention level):	Toxicological category 3 (Potent toxic material)
Other information:	**INN:** Dronabinol **Chemical names:** D9-THC, delta-9-THC, (6*aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol, Δ_9-tetrahydrocannabinol (D9-THC, Delta-9-tetrahydrocannabinol), (6aR)-*trans*-6,6,9-trimethyl-3-pentyl-(6ar,10at)-6,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol **Structure:**  **Molecular formula:** $C_{21}H_{30}O_2$ **Molecular mass:** 314.47 g/mol **Type of substance:** Controlled substance **Dissociation constant (pKa):** 10.6 **Partition coefficient:** Octanol-water: 1 at pH 7 **Hygroscopicity:** As Dronabinol is insoluble and not miscible with water, no hygroscopic effects are expected or known. **Chirality/Specific optical rotation:** Dronabinol (D9-THC) bears two stereogenic centers. Therefore, four stereoisomers are possible for this drug substance. Due to its manufacturing process only the (6a*R*, 10a*R*)-isomer can be obtained. The correct stereochemistry was confirmed by analytical control of the used starting materials menthadienol and olivetol and determination of enantiomeric purity of the intermediate D9-THC-Naphthoylester, which was 100 % enantiomeric pure. The specific optical rotation of Dronabinol (D9-THC), was found to be [α]= -150° (c = 1 in $CHCl_3$) and aligns with the literature. **Boiling point:** 155 – 157 °C / 0.05 Torr [2]

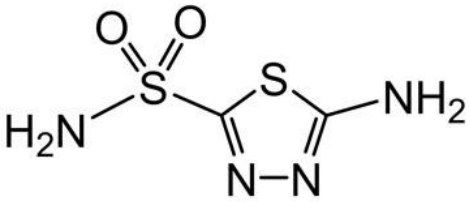
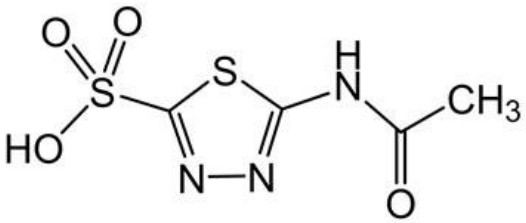
3. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGRIDIENT (API) (Acetazolamide)

Common name:	Acetazolamide
CAS number:	59-66-5 [4]
Description:	White to faintly yellowish-white, crystalline, odorless powder. [5]
Solubility:	Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water. [5]
Melting point:	258 – 259 °C [6]
Polymorphs:	Acetazolamide exists in two polymorphic forms, A and B, with one molecule in the asymmetric unit. In both polymorphs, the molecules establish hydrogen-bonded centrosymmetric dimers. The two forms differ distinctly

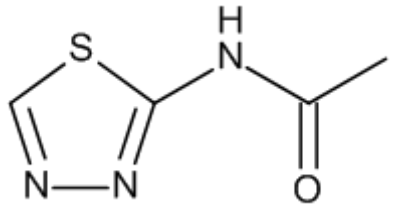
3. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGRIDIENT (API) (Acetazolamide)

	in the spatial arrangement of these pairs and the hydrogen bonds formed between them. Form A (mod. II, triclinic form) is the thermodynamically stable modification at 20 °C and is enantiotropically related to form B (mod. I, monoclinic form). The thermodynamic transition point lies between 120 and 148 °C. The solid-state properties of acetazolamide are mainly directed by the strong intermolecular hydrogen bond forces. Thus, the metastable form B exhibits a higher density than form A and a very high kinetic stability at 20 °C. Both forms can be crystallized from water and the solubility differences are very small, so, in addition to form A, the metastable but extremely resistant form B is suggested to be suitable for use in solid pharmaceutical formulations. The free energy change for acetazolamide polymorphic forms is 357 J/mol, which is a relatively small value. Therefore, it is presumed that acetazolamide polymorphic forms would not significantly affect bioavailability. [7, 8, 9]
Stability (Solid state/solution, general information):	As powder, Acetazolamide is stable under normal temperatures and pressures. It is sensitive to light [4, 6]
Scheme of degradation route:	Acetazolamide was found to be photolabile under irradiation with UV-B (at 300 nm) light under aerobic conditions. Photogradation of acetazolamide with UV-A light (at 337 nm, N_2 laser) as well as its photosensitizing degradation by rose bengal has been observed. Two photoproducts were isolated and identified, that were found to be identical in both conditions. Sensitization reaction involving singlet oxygen leads to the decomposition of acetazolamide. Direct electron transfer from the excited state of acetazolamide to the substrate occurs; specualiting that the superoxide molecule could be involved as an intermediate when the oxygen is present. The reaction scheme for conversion of acetazolamide to photoproducts is shown below. [10, 11] 

3. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGRIDIENT (API) (Acetazolamide)

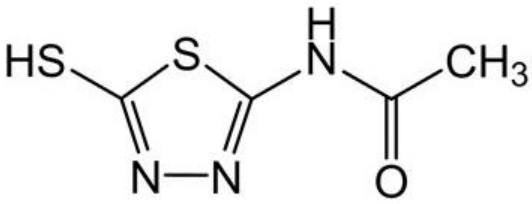
Stability indicators:	During the validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in a suspension (25 mg/mL), recovery values of 102 %, 103 %, 73 %, and 92 % were observed for four solutions prepared by mixing a 0.5-mL aliquot in water, aqueous hydrogen peroxide 3 %, aqueous sodium hydroxide 1 M and aqueous hydrochloric acid 1 M, respectively, after being stored for 3 h at 60 °C. [12] In forced degradation studies, it was found that acetazolamide suffered acid (97.0 %), base (94.4 %), and peroxide (96.1 %) degradation and resisted photolytic (100.1 %) and thermal degradation (99.6 %). In all the conditions, impurities B, D, E, and F were detected and quantified. [13] Degradation was not observed in acetazolamide stressed samples subjected to light (10 days, 98.6 %) and heat (60 °C, 98.5 %). Significant degradation of the drug substance and product was detected under acid (1 M HCl for 24 h, 94.2 %) and base hydrolysis (1 M NaOH for 24 h, 92.5 %), leading to the formation of one major unknown degradation product at 0.29 RRT (N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-amine). [14] In another study, acetazolamide was forced to degrade under oxidative, acidic, alkaline, photolytic, and thermal stress conditions. After the forced degradation when acetazolamide was analyzed, it was observed that there was no degradation during thermal and photolytic stress conditions. On the other hand, in the case of acidic and alkaline stress conditions, peaks of 7 degradation products at different retention times along with the peak of API were found. Also, under oxidative stress conditions, there were 3 degradation products. [15]
Impurities (Synthetic origin, degradation products and/or metabolites):	Impurity: Desacetyl acetazolamide (5-amino-1,3,4-thiadiazole-2-sulfonamide)  CAS No. 14949-00-9 Chemical formula: $C_2H_4N_4O_2S_2$ Molecular mass: 180.2 g/mol [16, 17] Impurity: Acetazolamide acid analog (5-acetamido-1,3,4-thiadiazole-2-sulfonic acid)  CAS No. 827026-60-8 Chemical formula: $C_4H_5N_3O_4S_2$ Molecular mass: 223.2 g/mol [16, 18] Impurity: Acetamidothiadiazole (N-(1,3,4-thiadiazol-2-yl)acetamide)

3. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGRIDIENT (API) (Acetazolamide)



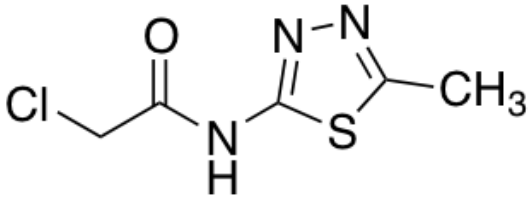
CAS No. 5393-55-5
Chemical formula: $C_4H_5N_3OS$
Molecular mass: 143.2 g/mol [16, 19]

Impurity: Mercaptothiazole analog (N-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide)



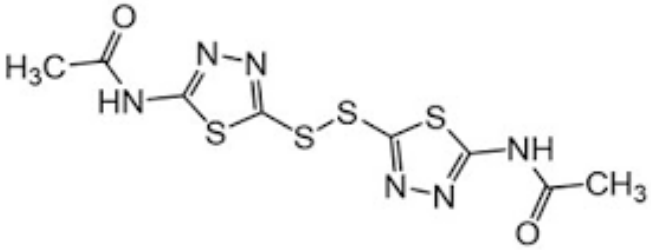
CAS No. 32873-56-6
Chemical formula: $C_4H_5N_3OS_2$
Molecular mass: 175.2 g/mol [16, 20]

Impurity: Chlorothiadiazole analog (N-5-chloro-1,3,4-thiadiazol-2-yl)acetamide)



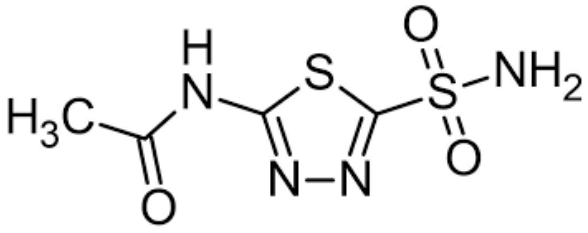
CAS No. 60320-32-3
Chemical formula: $C_4H_4ClN_3OS$
Molecular mass: 177.6 g/mol [16, 21]

Impurity: Acetazolamide dimer (N,N′-{5,5′-[(hydrosulfonylamino)sulfonyl]bis(1,3,4-thiadiazole-5,2-diyl)}diacetamide)



CAS No. 99055-56-8
Chemical formula: $C_8H_8N_6O_2S_4$
Molecular mass: 348.4 g/mol [16, 22]

3. GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGRIDIENT (API) (Acetazolamide)

Biopharmaceutical classification (Biopharmaceutical classification system):	Class IV [23]
Toxicological classification (Contention level):	Toxicological category 3 (Potent toxic material)
Other information:	**INN:** Acetazolamide **Chemical names:** N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide; N-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-acetamide; 5-acetamido-1,3,4-thiadiazole-2-sulfonamide **Structure:**  **Molecular formula:** $C_4H_6N_4O_3S_2$ **Molecular mass:** 222.3 g/mol **Dissociation constant (pKa):** 10.6 **Partition coefficient:** log P (octanol/water) value of -0.26 **pKa:** Acetazolamide is a weak acid with a pKa value of 7.2. **Stereoisomers:** No stereoisomerism is shown. [1, 24]

4. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

Brand name/Generic name	Marinol® (Dronabinol capsules, USP) [25]

Manufacturer	Patheon Softgels Inc. [25]
API	Dronabinol (UNII: 7J8897W37S) [25]
Excipients	Each Marinol® capsule strength is formulated with the following inactive ingredients: **2.5 mg capsule contains:** Gelatin, Unspecified (UNII: 2G86QN327L) Glycerin (UNII: PDC6A3C0OX) Sesame Oil (UNII: QX10HYY4QV) Titanium Dioxide (UNII: 15FIX9V2JP) **5 mg capsule contains:** Gelatin, Unspecified (UNII: 2G86QN327L)

4. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

	Glycerin (UNII: PDC6A3C0OX) Sesame Oil (UNII: QX10HYY4QV) Ferric Oxide Red (UNII: 1K09F3G675) Ferrosoferric Oxide (UNII: XM0M87F357) Titanium Dioxide (UNII: 15FIX9V2JP) **10 mg capsule contains:** Gelatin, Unspecified (UNII: 2G86QN327L) Glycerin (UNII: PDC6A3C0OX) Sesame Oil (UNII: QX10HYY4QV) Titanium Dioxide (UNII: 15FIX9V2JP) Ferric Oxide Red (UNII: 1K09F3G675) Ferric Oxide Yellow (UNII: EX438O2MRT) [25]
Strength(s)	2.5 mg 5 mg 10 mg [25]
Type of packaging material	Carton containing an amber glass bottle (with plastic cap and seal) and a package insert.
How supplied	**Marinol® (dronabinol capsules, USP) 2.5 mg:** Bottle x 60 capsules (NDC 53097-571-60) **Marinol® (dronabinol capsules, USP) 5 mg:** Bottle x 60 capsules (NDC 53097-572-60) **Marinol® (dronabinol capsules, USP) 10 mg:** Bottle x 60 capsules (NDC 53097-573-60) [25]
Physical characteristics (Color, size, shape, text printed, etc.)	**Marinol® (dronabinol capsules, USP) 2.5 mg** Color: White Size: 8 mm Shape: Round Imprint code: M2 Die roll: 3 round A STD **Marinol® (dronabinol capsules, USP) 5 mg** Color: Brown Size: 8 mm Shape: Round Imprint code: M5 Die roll: 3 round A STD **Marinol® (dronabinol capsules, USP) 10 mg** Color: Orange Size: 8 mm Shape: Round Imprint code: MX Die roll: 3 round A STD [25]
Expiration time	24 months
Storage conditions	Store in a cool environment between 8 and 15 °C (46 and 59 °F) and alternatively store in a refrigerator. Protect from freezing. [25]
Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.)	Dronabinol, the active ingredient in Marinol® (dronabinol capsules, USP), is synthetic delta-9- tetrahydrocannabinol (delta-9-THC). Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7. [25]

4. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

Manufacturing process information (Controls, recommended process conditions):	Data not available.

Observations:

(Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)

1. Based on the experience gained with the manufacturing of a generic version of Marinol® in Procaps, the following information related to the manufacturing and handling of Dronabinol Capsules is useful and should be considered when developing Dronabinol + Acetazolamide Unigel:

A. Dronabinol in Sesame Oil (~20 % w/w) should be handled under an argon atmosphere and should be kept at a temperature between 2 °C and 8 °C.
B. Dronabinol in Sesame Oil (~20 % w/w) should not be kept at room temperature for more than 3 hours.
C. Dispensing of Dronabinol in Sesame Oil (~20 % w/w) is supervised and controlled by a representative of the *Fondo Nacional de Estupefacientes* (National Fund of Narcotics in English).
D. Dronabinol in Sesame Oil (~20 % w/w) should be dispensed in amber glass containers inside a glove box cabinet.
E. Dispensing of Dronabinol in Sesame Oil (~20 % w/w) should be performed by applying the following procedures: SOP-1238, Dispensing of the Raw Material Dronabinol in Sesame Oil (~20 % w/w), INST-0805, Washing of Glass Containers used for the Weighing of Dronabinol, and INST-0627, Use and Operation of the Glove Box Cabinet.
F. The equipment and utensils used during the manufacturing of the Dronabinol fill solution should be dedicated.
G. During the manufacturing and storage of Dronabinol fill solution, the temperature should be kept between 8° and 12 °C and the pressure of argon should be maintained between 7 and 10 psi.
H. During the dispensing, manufacturing of Dronabinol fill solution, and encapsulation, sodium lights should be on.
I. The parts and utensils used during the encapsulation of the Dronabinol fill solution should be dedicated.

2. Dissolution method [26, 27]:

Drug name	Dosage form	USP apparatus	Speed (rpm)	Medium	Volume (mL	Recommended sampling times (minutes)
Dronabinol	Capsule	Refer to USP	Refer to USP	Refer to USP	Refer to USP	5, 10, 15, 30, 45, 60, and until at least 80% of the labeled content is released.

3. Inactive ingredient list [28]:

Marinol® (dronabinol capsules, USP) 2.5 mg						
Inactive ingredient	**Route; dosage form**	**CAS number**	**Unique ingredient identifier (UNII)**	**Maximum potency per unit dose**	**Maximum daily exposure (MDE)**	**Observations**
Gelatin, Unspecified	Oral, capsule, liquid filled	9000708	2G86QN327L	-	1,042 mg	None
Glycerin	Oral; capsule	56815	PDC6A3C0OX	-	3,487 mg	None
Sesame Oil	Oral; capsule	8008740	QX10HYY4QV	-	2,325 mg	None
Titanium Dioxide	Oral; capsule, liquid filled	13463677	15FIX9V2JP	-	12 mg	None

4. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

Marinol® (dronabinol capsules, USP) 5 mg						
Inactive ingredient	**Route; dosage form**	**CAS number**	**Unique ingredient identifier (UNII)**	**Maximum potency per unit dose**	**Maximum daily exposure (MDE)**	**Observations**
Gelatin	Oral, capsule, liquid filled	9000708	2G86QN327L	-	1,042 mg	None
Glycerin	Oral; capsule	56815	PDC6A3C0OX	-	3,487 mg	None
Sesame Oil	Oral; capsule	8008740	QX10HYY4QV	-	2,325 mg	None
Titanium Dioxide	Oral; capsule, liquid filled	13463677	15FIX9V2JP	-	12 mg	None
Ferric Oxide Red	Oral; capsule, liquid filled	1309371	1K09F3G675	1.21 mg	-	None
Ferrosoferric Oxide	Oral; capsule	1317619	XM0M87F357	-	1 mg	None

Marinol® (dronabinol capsules, USP) 10 mg						
Inactive ingredient	**Route; dosage form**	**CAS number**	**Unique ingredient identifier (UNII)**	**Maximum potency per unit dose**	**Maximum daily exposure (MDE)**	**Observations**
Gelatin	Oral, capsule, liquid filled	9000708	2G86QN327L	-	1,042 mg	None
Glycerin	Oral; capsule	56815	PDC6A3C0OX	-	3,487 mg	None
Sesame Oil	Oral; capsule	8008740	QX10HYY4QV	-	2,325 mg	None
Titanium Dioxide	Oral; capsule, liquid filled	13463677	15FIX9V2JP	-	12 mg	None
Ferric Oxide Red	Oral; capsule, liquid filled	1309371	1K09F3G675	1.21 mg	-	None
Ferric Oxide Yellow	Oral; capsule, liquid filled	51274001	EX438O2MRT	-	1 mg	None

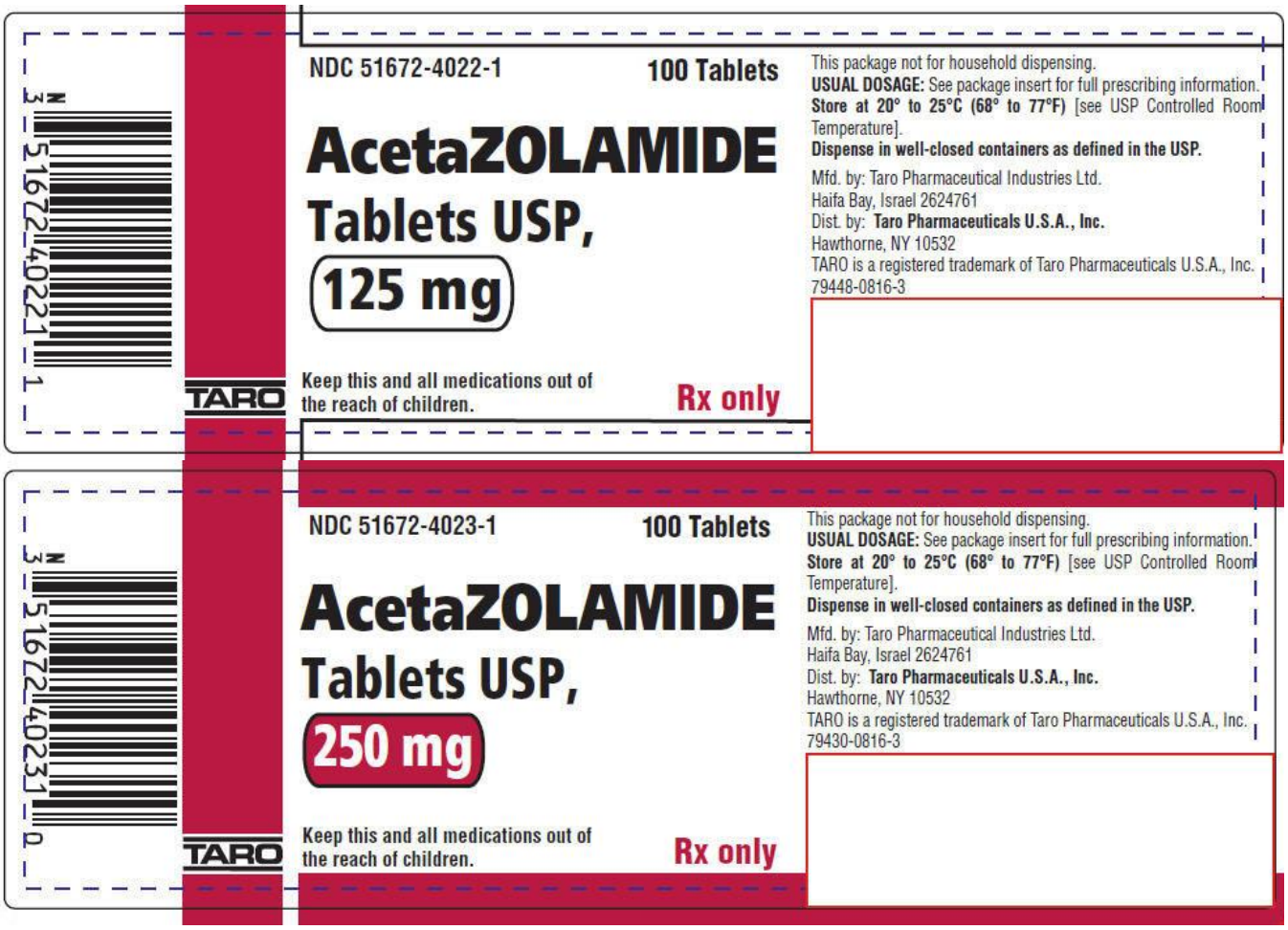
4. **Bioequivalence recommendations:** Bioequivalence are not necessary. The product to be developed contains a new drug combination (dronabinol and acetazolamide) and uses a new dosage form (Unigel). Since the new product is innovative, clinical studies will be performed. Incannex Healthcare Limited will seek approval of an NDA to market the new product in the US.

5. **Packaging:** Although Marinol® (dronabinol capsules, USP) is packaged in amber glass bottles, the packaging material of the product to be developed (NDA) will be different. Incannex Healthcare Limited asked for blister packs to be used as packaging materials.

5. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

Brand name/Generic name	Acetazolamide Tablets USP [29]



Manufacturer	Taro Pharmaceutical Industries Ltd. [29]
API	Acetazolamide (UNII: O3FX965V0I) [29]
Excipients	Lactose Monohydrate (UNII: EWQ57Q8I5X) Starch, Corn (UNII: O8232NY3SJ) Gelatin, Unspecified (UNII: 2G86QN327L) Glycerin (UNII: PDC6A3C0OX) Water (UNII: 059QF0KO0R) Talc (UNII: 7SEV7J4R1U) Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2) Magnesium Stearate (UNII: 70097M6I30) [29]
Strength(s)	125 mg 250 mg [29]

5. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

Type of packaging material	Plastic bottle with a package insert.
How supplied	**Acetazolamide Tablets USP 125 mg:** Bottle x 100 tablets (NDC 51672-4022-1) **Acetazolamide Tablets USP 250 mg:** Bottle x 100 tablets (NDC 51672-4023-1) [29]
Physical characteristics (Color, size, shape, text printed, etc.)	**Acetazolamide Tablets USP 125 mg:** **Color:** White **Size:** 9 mm **Shape:** Round **Score/Imprint code:** Scored in half, on one side, "T52" engraved on the other side. **Acetazolamide Tablets USP 250 mg:** **Color:** White **Size:** 9 mm **Shape:** Round **Score/Imprint code:** Scored in quarters, on one side, "T53" engraved on the other side. [29]
Expiration time	Data not available
Storage conditions	Store at 20° to 25°C (68° to 77°F) [29]
Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.)	Acetazolamide Tablets, USP from Pharmaceutical Industries Ltd. contain gelatin and glycerin. Gelatin has been used as a binder and a coating agent while Glycerin has been used as a solvent and binding enhancer in tablet manufacturing. The function of both excipients in the formulation must be studied. [30]
Manufacturing process information (Controls, recommended process conditions):	Data not available.

Observations:

(Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)

1. **Sodium lights should be used throughout the manufacturing process of Acetazolamide coated tablets, especially during mixing, granulation, and tableting stages, since Acetazolamide is sensitive to light.** [4]

2. **Dissolution method [27, 31]:**

Drug name	Dosage form	USP apparatus	Speed (rpm)	Medium	Volume (mL	Recommended sampling times (minutes)
Acetazolamide	Tablet	Refer to USP	Refer to USP	Refer to USP	Refer to USP	-

5. INFORMATION OF THE REFERENCE LISTED DRUG (RLD)

(The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book)

3. Inactive ingredient list [28]:

Acetazolamide Tablets USP 125 mg / 250 mg						
Inactive ingredient	**Route; dosage form**	**CAS number**	**Unique ingredient identifier (UNII)**	**Maximum potency per unit dose**	**Maximum daily exposure (MDE)**	**Observations**
Lactose Monohydrate	Oral, tablet, coated	64044515	EWQ57Q8I5X	-	1,002 mg	None
Starch, Corn	Oral, tablet, coated	9005258	O8232NY3SJ	285 mg	-	None
Gelatin, Unspecified	Oral, tablet, coated	9000708	2G86QN327L	42.12 mg	-	None
Glycerin	Oral, tablet, coated	56815	PDC6A3C0OX	1 mg	-	None
Water	Oral, tablet, coated	-	-	-	-	None
Talc	Oral, tablet, coated	14807966	7SEV7J4R1U	320.75 mg	-	None
Sodium Starch Glycolate Type A	Oral, tablet, coated	9063381	H8AV0SQX4D	73 mg	-	None
Magnesium Stearate	Oral, tablet, coated	557040	70097M6I30	-	184 mg	None

4. **Bioequivalence recommendations:** Bioequivalence studies are not necessary. The product to be developed contains a new drug combination (dronabinol and acetazolamide) and uses a new dosage form (Unigel). Since the new product is innovative, clinical studies will be performed. Incannex Healthcare Limited will seek approval of an NDA to market the new product in the US.

5. **Packaging:** Although Acetazolamide Tablets USP from taro Pharmaceuticals Ltd. are packaged in plastic bottles, the packaging material of the product to be developed (NDA) will be different. Incannex Healthcare Limited asked for blister packs to be used as packaging materials.

6. INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS

Official monographs for the API:	Dronabinol USP monograph [32] Acetazolamide USP monograph [16] Acetazolamide Ph. Eur. monograph [33] Acetazolamide BP monograph [34] Acetazolamide JP monograph [35]
Official monographs for the finished products:	Dronabinol, capsules USP monograph [26] Acetazolamide, tablets USP monograph [31] Acetazolamide, tablets BP monograph [36]

Other information:

1. API monographs

Dronabinol USP monograph [32]		
Description: Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. **Solubility:** Insoluble water.		
Test	**Acceptance criteria**	**Observations**
Identification A	The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.	Chromatography ⟨621⟩: Liquid Chromatography
Identification b	The color and *R*F value of the spots from the *Test solution* correspond to those obtained from the *Identification solution*.	Chromatography ⟨621⟩: Thin-layer Chromatography
Related compounds	Cannabinol: Not more than 1.5 %. *Exo*-tetrahydrocannabinol: Not more than 0.5 %. Δ^8-Tetrahydrocannabinol: Not more than 2.0 %. Any other individual impurity: Not more than 1.0 %. Total impurities: Not more than 5.0 %.	Chromatography ⟨621⟩: Liquid Chromatography
Assay	Not less than 95.0 percent of $C_{21}H_{30}O_2$.	Chromatography ⟨621⟩: Liquid Chromatography

Acetazolamide USP monograph [16]		
Description: White to faintly yellowish-white, crystalline, odorless powder. **Solubility:** Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water.		
Test	**Acceptance criteria**	**Observations**
Identification A	The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*.	Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K
Identification b	The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.	Chromatography ⟨621⟩: Liquid Chromatography
Assay	98.0 % – 102.0 % on the anhydrous basis	Chromatography ⟨621⟩: Liquid Chromatography
Residue on ignition ⟨281⟩	Not more than 0.1 %	None
Chloride	A 25-mL portion of the filtrate shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid 0.014%).	Chloride and Sulfate ⟨221⟩
Sulfate	It shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (0.04%).	Chloride and Sulfate ⟨221⟩
Selenium ⟨291⟩	Not more than 30 rpm.	None

6. INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS

Test	Acceptance criteria	Observations
Organic impurities	Desacetyl acetazolamide: Not more than 0.3 %. Acetazolamide acid analog: Not more than 0.5 %. Acetamidothiadiazole: Not more than 0.5 %. Mercaptothiadiazole analog: Not more than 0.5 %. Chlorothiadiazole analog: Not more than 0.5 %. Acetazolamide dimer: Not more than 0.5 %. Any unspecified impurity: Not more than 0.1 %. Total impurities: Not more than 1.0 %.	Chromatography ⟨621⟩: Liquid Chromatography

Acetazolamide BP monograph / Ph. Eur. monograph 0454 [33, 34]		
Test	**Acceptance criteria**	**Observations**
Appearance	White or almost white, crystalline powder.	None
Solubility	Very slightly soluble in water, slightly soluble in ethanol (96 percent). It dissolves in dilute solutions of alkali hydroxides.	None
Identification A	The UV absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide.	Ultraviolet and visible absorption spectrophotometry (2.2.25)
Identification B	The infrared absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide.	Infrared absorption spectrophotometry (2.2.24)
Identification C	The paper shows a brownish-black color.	None
Identification D	A greenish-blue precipitate is formed.	None
Appearance of solution	The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely colored than reference solution Y_5 or BY_5 (2.2.2, Method II).	None
Related substances	Impurities A, B, C, D, E, F: For each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 percent) Unspecified impurities: For each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 percent) Total: Not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 percent)	None
Sulfates (2.4.13)	Maximum 500 ppm.	None
Loss on drying (2.2.32)	Maximum 0.5 percent	Determined on 1.000 g by drying in an oven at 105 °C.
Sulfated ash (2.4.14)	Maximum 0.1 percent	Determined on 1.0 g.
Assay	98.5 per cent to 101.0 per cent (dried substance)	Potentiometric titration (2.2.20)

Acetazolamide JP monograph [35]		
Test	**Acceptance criteria**	**Observations**
Description	Acetazolamide occurs as a white to pale yellowish white crystalline powder. It is odorless and has a slight bitter taste.	None
Solubility	It is slightly soluble in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether.	None
Melting point	About 255 °C (with decomposition).	None
Identification 1	A deep yellow color is produced gradually.	None
Identification 2	Responds to the Qualitative Tests ⟨1.09⟩ for primary aromatic amines.	None
Identification 3	The gas evolved darkens moistened lead (II) acetate paper.	None
Clarity and color of solution	The solution is clear and colorless to pale yellow	None

6. INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS

Test	Acceptance criteria	Observations
Chloride ⟨1.03⟩	Not more than 0.014 %.	None
Sulfate ⟨1.14⟩	Not more than 0.038 %.	None
Heavy metals ⟨1.07⟩	Not more than 20 ppm.	None
Silver-reducing agents	Not less than 4.8 mL of 0.1 mol/L ammonium thiocyanate VS is consumed	Titration ⟨2.50⟩
Loss on drying (2.41)	Not more than 0.5 %.	Determined on 0.5 g, 105 °C, 3 hours.
Residue on ignition (2.44)	Not more than 0.1 %.	Determined on 0.5 g.
Assay	Not less than 98.0 % and not more than 102.0 % of acetazolamide (C4H6N4O3S2), calculated on the dried basis.	Ultraviolet-visible Spectrometry ⟨2.24⟩

2. Drug product monographs

Dronabinol, capsules USP monograph [26]		
Test	**Acceptance criteria**	**Observations**
Identification	The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.	Chromatography ⟨621⟩: Liquid Chromatography
Assay	Not less than 90.0 % and not more than 110.0 % of the labeled amount of dronabinol ($C_{21}H_{30}O_2$).	Chromatography ⟨621⟩: Liquid Chromatography
Dissolution ⟨711⟩	The requirements are met if all of the capsules tested rupture in NMT 15 min. If 1 or 2 of the capsules rupture in NLT 15 but NMT 30 min, repeat the test on 12 additional Capsules. NMT 2 of the total of 18 capsules tested rupture in NLT 15 min but NMT 30 min.	Medium: Water Volume: 500 mL Apparatus: 2 Speed: 50 rpm Time: 15 minutes
Uniformity of Dosage Units ⟨905⟩	Meet the requirements.	None

Acetazolamide tablets, USP monograph [31]		
Test	**Acceptance criteria**	**Observations**
Identification A	The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*.	Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K
Identification b	The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.	Chromatography ⟨621⟩: Liquid Chromatography
Assay	95.0 % - 105.0 %	Chromatography ⟨621⟩: Liquid Chromatography
Dissolution ⟨711⟩	NLT 75% (*Q*) of the labeled amount of acetazolamide ($C_4H_6N_4O_3S_2$) is dissolved.	Medium: 0.01 N HCl Volume: 900 mL Apparatus: 1 Speed: 100 rpm Time: 60 minutes
Uniformity of Dosage Units ⟨905⟩	Meet the requirements.	None

Acetazolamide tablets, BP monograph [36]		
Test	**Acceptance criteria**	**Observations**
Identification A	The infrared spectrum of the residue is concordant with the reference spectrum of acetazolamide.	Infrared spectrometry

6. INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS

Test	Acceptance criteria	Observations
Identification b	The paper exhibits a brownish black color.	None
Identification b	A greenish blue color or precipitate is produced.	None
Related substances	Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1 %).	Thin-layer chromatography
Assay	95.0 to 105.0 % of the stated amount of acetazolamide.	Potentiometric titration

7. REVISION OF PATENTS (BACKGROUND AND RESTRICTIONS)

See patent revision report.

8. REFERENCES (Specify the references throughout the document with numbers between brackets i.e. [1])

[1] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 16078, Dronabinol. Retrieved January 4, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol.
[2] Dronabinol in Sesame Oil, Product Technical Package, US DMF # 20682, Purisys™.
[3] Ronak Savla, Jeff Browne, Vincent Plassat, Kishor M. Wasan & Ellen K. Wasan (2017) Review and analysis of FDA approved drugs using lipid-based formulations, Drug Development and Industrial Pharmacy, 43:11, 1743-1758.
[4] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 1986, Acetazolamide. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/Acetazolamide.
[5] Reference tables: USP. Description and Relative Solubility of USP and NF Articles. In USP-NF. Rockville, MD: USP; January 5, 2022.
[6] ChemSpider (2022). Chemical Structure Search, Acetazolamide. Retrieved January 5, 2022, from http://www.chemspider.com/Chemical-Structure.1909.html.
[7] Griesser, U. J., Burger, A., & Mereiter, K. (1997). The Polymorphic Drug Substances of the European Pharmacopoeia. Part 9. Physicochemical Properties and Crystal Structure of Acetazolamide Crystal Forms. Journal of Pharmaceutical Sciences, 86(3), 352–358.
[8] Umeda, T., Ohnishi, N., YokoyamA, T., Kuroda, T., Kita, Y., Kuroda, K., Matsuda, Y. (1985). Physico-chemical properties and isothermal transition of acetazolamide polymorphs. Chemical & Pharmaceutical Bulletin, 33(8), 3422–3428.
[9] Baraldi, C., Gamberini, M. C., Tinti, A., Palazzoli, F., & Ferioli, V. (2009). Vibrational study of acetazolamide polymorphism. Journal of Molecular Structure, 918(1-3), 88–96.
[10] Zaheer, M. *et al*. Molecular Mechanisms of Drug Products Photodegradation and Photosensitization. Current Pharmaceutical Design, 2016, 22, 768-782.
[11] Vargas, F., Hisbeth, M. V., & Rojas, J. K. (1998). Photolysis and photosensitized degradation of the diuretic drug acetazolamide. Journal of Photochemistry and Photobiology A: Chemistry, 118(1), 19–23.
[12] Friciu, M., Abatzoglou, N., & Leclair, G. (2020). Validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in Oral-Mix and Oral-Mix SF. MethodsX, 7, 100844.
[13] Suresh, P., Lavakesh, O., Pushpendra S. (2020). Development and Validation of Stability Indicating Related Substance Method for Acetazolamide Tablets. Journal of Medical Pharmaceutical and Allied Sciences. 9(I3), 951, 2518-2526.
[14] Srinivasu, P., SubbaRao, D. V., Vegesna, R. V. K., & Sudhakar Babu, K. (2010). A validated stability-indicating LC method for acetazolamide in the presence of degradation products and its process-related impurities. Journal of Pharmaceutical and Biomedical Analysis, 52(1), 142–148.
[15] Manchanda, S., Sahoo, P., Majumdar, D. (2016). RP-HPLC method development and validation for the estimation of Acetazolamide in bulk drug and formulations with forced degradation studies. Der Pharmacia Lettre, 8(1), 338-347.
[16] Monograph: USP. Acetazolamide. In USP-NF. Rockville, MD: USP; 2022.
[17] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 84724, 5-Amino-1,3,4-thiadiazole-2-sulfonamide. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/5-Amino-1_3_4-thiadiazole-2-sulfonamide.

[18] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 56924023, 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/5-Acetamido-1_3_4-thiadiazole-2-sulfonic-acid.
[19] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 94839, n-(1,3,4-Thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/n-_1_3_4-Thiadiazol-2-yl_acetamide.
[20] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 2723687, 2-Acetylamino-5-mercapto-1,3,4-thiadiazole. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/2-Acetylamino-5-mercapto-1_3_4-thiadiazole.
[21] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 314332, N-(5-chloro-1,3,4-thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/N-_5-chloro-1_3_4-thiadiazol-2-yl_acetamide.
[22] National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 331896. Retrieved January 5, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/331896.
[23] Santoveña, A., Suárez-González, J., Martín-Rodríguez, C., & Fariña, J. B. (2016). Formulation design of oral pediatric Acetazolamide suspension: dose uniformity and physico-chemical stability study. Pharmaceutical Development and Technology, 22(2), 191–197.
[24] Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: acetazolamide. J Pharm Sci. 2008 Sep;97(9):3691-9.
[25] The PharmaNetwork, LLC. Marinol® (dronabinol capsules, USP). 2021 [rev. 2021 March; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d0efeeec-640d-43c3-8f0a-d31324a11c68.
[26] Monograph: USP. Dronabinol, capsules. In USP-NF. Rockville, MD: USP; 2022.
[27] FDA-Recommended Dissolution Methods Database. Retrieved January 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm.
[28] FDA-Inactive Ingredient Search for Approved Drug Products. Retrieved January 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.
[29] Taro Pharmaceuticals U.S.A., Inc. 2016 [rev. 2016 September; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9.
[30] Rowe, R. C., Sheskey, P. J., & Weller, P. J. (2003). Handbook of pharmaceutical excipients. London: Pharmaceutical Press.
[31] Monograph: USP. Acetazolamide, tablets. In USP-NF. Rockville, MD: USP; 2022.
[32] Monograph: USP. Dronabinol. In USP-NF. Rockville, MD: USP; 2022.
[33] Monograph: Ph. Eur. Acetazolamide. In *European pharmacopoeia*. Strasbourg: Council of Europe; 2022.
[34] Monograph: BP. Acetazolamide. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022.
[35] Monograph: JP. Acetazolamide. In *The Japanese pharmacopoeia*. Tokyo: Society of Japanese Pharmacopoeia; 2022.
[36] Monograph: BP. Acetazolamide tablets. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022.

9. ANNEXES

ANNEX	DESCRIPTION
1	IHL-42X formulation brief August 2021

10. RELATED DOCUMENTS

CODE	DESCRIPTION
-	Statement of Work (SOW)
1972-08-3	API Toxicological Characterization Phase IB: Dronabinol
59-66-5	API Toxicological Characterization Phase IB: Acetazolamide
SOP-1238	Dispensing of Dronabinol in Sesame Oil (~20 % w/w) Raw Material
INST-0805	Washing of Glass Containers used for the Weighing of Dronabinol
INST-0627	Use and Operation of the Glove Box Cabinet

11. AUTHORIZATIONS

PERFORMED BY:			REVIEWED BY:			APPROVED BY:	
Name:	Jefferson Castro	Juan Estrada	Name:	Jabid Lotero	Rahumir Gutiérrez	Name:	Henry Herrera
Job title:	Analyst III	Technical Formulator	Job title:	Head of Product Development (ad. int.)	Head of Product Development	Job title:	Research and Development Director (ad. int.)
Area:	R&D	R&D	Area:	R&D	R&D	Area:	R&D
Signature:			Signature:			Signature:	
Date:			Date:			Date:	