TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR INTAS (BICALUTAMIDE 50MG) FILM COATED TABLETS

Version number 1.0

14th April, 2022

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1. Introduction

INTAS Bicalutamide is a generic medicine of CASODEX® of AstraZeneca. INTAS Bicalutamide is an anticancer medicine belonging to Antineoplastic and Immunomodulating Agents, Anti-androgens group. INTAS Bicalutamide exerts is activity by binding to androgen receptors without activating gene expression, and thus inhibits the androgen stimulus.
INTAS Bicalutamide is approved in Tanzania for use in adults and elderly.

1.1 Product details

Registration number	TAN 21 HM 0214
Brand name	INTAS Bicalutamide
Generic name, strength and form	Bicalutamide 50 mg film coated tablets
ATC classification	ATC code L02BB03 Anti-androgens
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	Intas Pharmaceuticals Limited Corporate House, Near Sola Bridge, S.G. Highway, Thaltej, Ahmedabad-380054, Gujarat, **INDIA.** Telephone: +9179 39837909 Email: alkesh_shah@intaspharma.com
Local Technical Representative	Lifeline Pharmacy Ltd Plot no. 540, Kalenga Street, Upanga, P.O. BOX 76969, Dar esSalaam, **TANZANIA.** Telephone: **(255) 713244004** Email: lifelineupanga@gmail.com

1.2 Assessment procedure

The application for registration of INTAS Bicalutamide was submitted on 10th October, 2018. The product underwent joint EAC assessment. Assessment was completed in 2 rounds of evaluation. INTAS Bicalutamide was registered on <03rd June 2021

1.3 Information for users

Visual description of the finished product	White to off white, round, biconvex, film coated tablets debossed 'B 50' on one side and plain on other side.
Primary packing material	Clear PVC/PVdC-Alu blister
Secondary packing materials	Cardboard carton box

Shelf-life and storage condition	24 months, Store in dry place below 30 °C
Route of administration	Oral
Therapeutic indications	Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC

Container labels
The product label information is presented in English. Details in the secondary pack label include:

Brand name: INTAS Bicalutamide

Composition: Bicalutamide 50 mg

Pack size: 2 x 14's

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store in dry place below 30 °C

Manufacturer address: Intas Pharmaceuticals Limited, Plot No. 457, 458, Village – Matoda, Bavla Road, Tal. Sanand, Dist, Ahmedabad – 382 210, Gujarat, India

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

The details of the primary pack include:
Brand name and strength: INTAS Bicalutamide (Bicalutamide 50 mg)

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Intas Pharmaceuticals Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products.

The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are appended as annex I

3. Scientific discussion

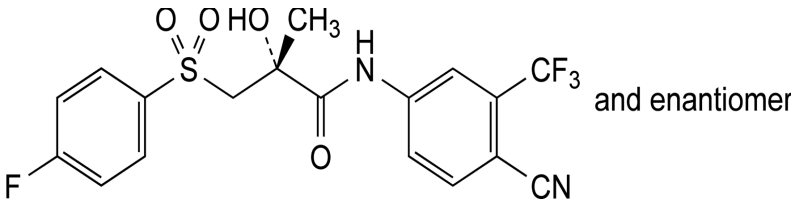
Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of CEP and Full details

General Information
Bicalutamide API is compendia in USP/BP
Molecular formula: $C_{18}H_{14}F_4N_2O_4S$

Chemical name: (2RS)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide

Structure:



and enantiomer

Physico-chemical properties of the API
Bicalutamide is a white powder that is practically insoluble in water, freely soluble in acetone, slightly soluble in anhydrous ethanol and in methylene chloride. The drug substance is non hygroscopic. Bicalutamide occurs a racemic mixture that contains 50/50 composition of (R)-bicalutamide and (S)-bicalutamide enantiomers, with its activity mostly contributed by the (R)-enantiomer. Bicalutamide exhibit polymorphism and polymorphic form 1 was consistently produced by both suppliers

Manufacture
The API manufacturing sites are: Hetero Labs Limited, Survey No. 10 , I.D.A, Gaddapotharam Village, Jinnaram Mandal, Sangareddy District, Telangana, India and MSN Laboratories Private Limited, MSN House, Plot No.: C-24, Sanath Nagar industrial Estate, Sanath Nagar,Hyderabad, Telangana – 500 018, India. The sites were noted to comply with GMP requirements as evidenced by the GMP certificates issued by Drug Control Administration Government of Telangana

Bicalutamide API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per BP, in-house standards and ICHQ3A. The parameters monitored during quality control are: appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC), optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), polymorphism (XRD), heavy metal (Ph. Eur), assay (HPLC), residual solvents (HS-GC), related substances (HPLC), acetic acid content (HPLC) and particle size distribution.
Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Bicalutamide API is 60 months when packed in polyethylene bags inside HDPE container and stored at 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

INTAS Bicalutamide is a White to off white, round, biconvex, film coated tablets debossed 'B 50' on one side and plain on other side. INTAS Bicalutamide contains Bicalutamide and other ingredients listed here after

Core tablets

Lactose Monohydrate
Sodium starch glycolate (Type A)
Povidone K-30
Purified water
Magnesium stearate

Film coating

Hypromellose
Titanium dioxide
Macrogol 400
Purified water

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, Lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at INTAS PHARMACEUTICALS LTD, Plot Nos. 457, 458 & 191/218P, Sarkhej-Bavla Highway, Matoda, Sanand, Ahmedabad, Gujarat, 382210, India. The

compliance of the site to TMDA GMP standards was confirmed through site inspection on 9th May 2019

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: Appearance (visual), average weight of tablets (Ph. Eur.), Uniformity of weight (Ph. Eur.), Disintegration time (Ph. Eur.), Identification (IR, HPLC), Loss on drying, Hardness (Ph. Eur.), Dissolution (HPLC), Related substances (HPLC), Uniformity of dosage units (Ph. Eur.), Assay (HPLC), Microbial limit test (Ph. Eur.). Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30°C ± 2°C, 75% ±5 % RH for 24 months and 40°C ± 2°C / 75% ±5 % RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in PVC/PVdC-Alu blisters at 30ºC

Safety and efficacy information

Safety and efficacy of INTAS Bicalutamide was established through bioequivalence trial
BE report number Project No. 124 – 06 was submitted.

Study title	Open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, cross over, comparative oral bioavailability study of Bicalutamide Tablets 50 mg in Healthy, Adult, Human male subjects under fasting condition.	
Study design	Open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, cross over	
Study site	Lambda Therapeutic Research Limited 7th Floor, The Great Eastern Summit-A, Plot No. 56, Sector 15, CBD Belapur, Navi Mumbai-400614, India	
Study dates	02 September 2006 to 06 January 2007	
Primary objective	To compare the bioavailability and characterize the pharmaceutic profile of the sponsor formulations with respect to the reference formulation Casodex 50 mg tablets in healthy adult human male subjects under fasting conditions and to assess the bioequivalence.	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects	
Number of participants	67 subjects enrolled 46 subjects dosed 39 subjects considered for pharmacokinetic and bioanalytical analysis	
Monitored parameters	C_{max}; $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$.	
Investigational medicinal products	Test Product	Reference product
	Strength: 50 mg	Strength: 50 mg

	Batch number: F4756 Expiry date: 09/2007	Batch number: GC11P2 Expiry date: 02/2019
Analytical method	LC-MS/MS	
Statistical method	WinNonlin Professional Software	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)	172378.989	191428.444	90.0	84.46 – 96.01	39	16.9
AUC0-inf (units)	189687.8666	215879.740	87.9	82.42 – 93.68	34	15.2
Cmax (units)	874.176	996.951	87.7	83.35 – 92.24	39	13.3

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, INTAS Bicalutamide Tablets 50 mg is equivalent and interchangeable with Casodex 50 mg under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. INTAS Bicalutamide Tablets 50 mg is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

NA

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label