Thai Food and Drug Administration (Thai FDA) public assessment report

Division for health products entrepreneurship promotion

Quality – generic without bioequivalent medicinal products

Ketromax Injection

Ketorolac Tromethamine 30 mg/ml, packing size 1 ml/ampoule

E-identifier Number: e6200107
Submission Number: 1C 15069/62 (NG)

Applicant: American Taiwan Biopharm Co., Ltd.

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Administrative information

Invented name of the medicinal product:	Ketromax® **(คีโทรแม็กซ์)**
INN (or common name) of the active substance(s):	Ketorolac Tromethamine
Applicant:	American Taiwan Biopharm Co., Ltd.
Applied Indication(s):	Ketorolac Injection is indicated for the short-term management of moderate to severe acute post-operative pain. Treatment should only be initiated in hospitals. The maximum duration of treatment is 5 days.
Pharmaco-therapeutic group (ATC Code):	Anti-inflammatory and Anti-rheumatic products, Non-steroid: (M01AB15)
Pharmaceutical form(s) and strength(s):	Solution for injection 30 mg/ml (1 ml)

1. Recommendation

Based on the review of the data on quality part, Thai FDA considers that the application of Ketromax could be approvable in indication, Ketorolac Injection is indicated for the short-term management of moderate to severe acute post-operative pain. Treatment should only be initiated in hospitals. The maximum duration of treatment is 5 days, as same as an approved original product (Ketolac®).

The original product of Ketorolac is Toradol®. In 2008, American Taiwan Biopharm has already got product licensed of Ketolac®, licensed number 1C 98/51 (NC), manufactured by Siu Guan Chem. Ind. Co., Ltd. American Taiwan Biopharm submitted all new application of Ketolac® into the new brand "Ketromax". Therefore, all information is the same as Ketolac® but updating for CMC. SMP is still necessary for Ketolac®.

Recommended conditions for marketing authorisation and product information

1.1 Conditions for the marketing authorisation

Medicinal product subject to extra conditions for the marketing authorisation is spontaneous monitoring product by reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Thai FDA.

1.2 Summary of product characteristics (SmPC)

Satisfactory, SmPC follows ASEAN harmonization and conforms to quality, non-clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC, promoting rational drug use.

1.3 Labelling

Satisfactory

1.4 Patient information leaflet (PIL)

Satisfactory

User consultation

The applicant must pass the user testing of PIL within 12 months after authorisation.

2. Executive summary

2.1 Problem statement

Pain is classified as acute and chronic pain. Acute pain is characterized as being of recent onset, transient, and usually from an identifiable cause. Chronic or persistent pain can be described as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury healing, more than 3 to 6 months, and which adversely affects the individual's well-being.

Nociceptive pain involves the normal neural processing of pain that occurs when free nerve endings are activated by tissue damage or inflammation. Tissue damage releases chemical mediators, such as prostaglandins, bradykinin, serotonin, substance P, and histamine. These substances then activate nociceptors, resulting in transduction, or the generation of an action potential (an electrical impulse).

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). It is a racemic mixture of the S- and R-enantiometric forms. Ketorolac tromethamine exhibits analgesic activity through its S-enantiomer. The analgesic mechanism of action is related to inhibition of cyclooxygenase which results in reduced synthesis of prostaglandins, thromboxanes, and prostacyclin. Ketorolac tromethamine does not possess any sedative or anxiolytic activities nor does it have any effect on gut motility.

The therapeutic indications of Ketorolac tromethamine are intended to be treatment of moderate to severe acute pain especially postoperative setting for short-term (up to 5 days in adults).

2.2 About the product

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). It is a racemic mixture of the S- and R-enantiometric forms. Ketorolac tromethamine exhibits analgesic activity through its S-enantiomer. The analgesic mechanism of action is related to inhibition of cyclooxygenase which results in reduced synthesis of prostaglandins, thromboxanes, and prostacyclin. Ketorolac tromethamine does not possess any sedative or anxiolytic activities nor does it have any effect on gut motility.

2.3 The development programme/compliance with Thai FDA guidance/scientific advice

Not applicable

2.4 General comments on compliance with GMP, GLP, GCP

GMP certificate from Siu Guan Chem. Ind. Co., Ltd is available and accepted by Thai FDA.

GMP clearance certificate is available and accepted by Thai FDA.

2.5 Type of application and other comments on the submitted dossier

Generic medicinal product without bioequivalent application
Ketromax is an intravenous injection dosage form. Hence, bioequivalence study is not required for Ketromax.
Marketing authorisation holder: American Taiwan Biopharm Co., Ltd., Thailand
Date of first authorisation in Taiwan (TFDA): 10/05/2005.

3. Quality assessment

3.1 Introduction

Name:	Ketorolac tromethamine
Dosage form and strength:	Injection 30 mg/ml
Procedure:	Generic medicinal product without bioequivalent
Therapeutic class or indication:	Anti-inflammatory and Anti-rheumatic products

The finished product is presented as sterile colorless to slightly yellow solution in transparent ampoule containing 30 mg/ml of Ketorolac tromethamine as active substance. Other ingredients are sodium chloride, ethanol, sodium hydroxide, hydrochloric acid and water for injection. The product is available in USP type I colorless and transparent ampoule, together

with a plastic ampoule tray and 1 package insert per individual box. One pack size (box) contains 10, 15, 20, 25 or 50 amps/box.

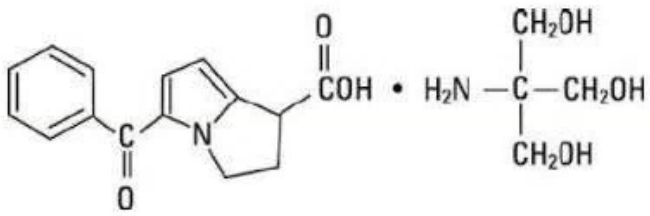
3.2 Drug substance (Ketorolac tromethamine)

3.2.1 General Information *(CTD module 3.2.S.1)*

S.1.1 Nomenclature *(CTD section: S.1.1)*

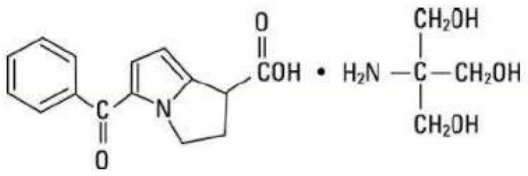
International non-proprietary name (INN):	Ketorolac tromethamine
Chemical names:	2-amino-2-(hydroxymethyl) propane-1,3-diol (1RS)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate
Molecular formula:	$C_{19}H_{24}N_2O_6$
Relative molecular mass:	376.4 g/mol

Structural formula (CTD section: S.1.2)



General properties *(CTD section: S.1.3)*

Physical characteristics:	A white to off white crystalline powder
Solubility:	Freely soluble in water and in methanol, slightly soluble in alcohol, in dehydrated alcohol and in tetrahydrofuran, practically insoluble in acetone, in dichloromethane, in toluene, in ethyl acetate, in dioxane, in hexane, in butyl alcohol and in acetonitrile.
Hygroscopicity:	Slightly hygroscopic in nature
Melting point	165°C – 170°C (with decomposition)
pH	Between 5.7 and 6.7

Structural formula	

Assessor's comments on S.1 General Information Documents in this part are acceptable.

3.2.2 Manufacture CTD module 3.2.S.2

Manufacturer(s) (CTD section: S.2.1)

The active drug substance Ketorolac tromethamine is manufactured in INDIA.

GMP

A GMP certificate, issued by Government of India, is attached.

Control of materials (CTD section: S.2.3)

The starting material, intermediates and reagent are well controlled, the applicant submitted CoA that the results are complying with specification.

Control of critical steps and intermediates (CTD section: S.2.4)

The degrading products and process related impurities are well controlled by the limitation of impurities, which tested by the HPLC method. The limitation of the degrading products and process related impurities are controlled at NMT 0.10%. The degrading products and process related impurities are consisting of 3 types;

1. Organic impurities in USP monograph
2. Additional impurities from API
3. Process related impurities

Process validation and/or evaluation (CTD section: S.2.5)

The applicant submitted CoA and the results of 3 consecutive batches are complying with specification.

Assessor's comments on S.2 Manufacture*:* Ketorolac tromethamine was manufactured in India. The manufacturer has valid GMP certified by Government of India, Ministry of health & Family welfare Central drugs standard control organization. Manufacturing process and quality control is suitable by identification of critical steps on process and control including process validation, so all of documents confirm that drug substance manufacturing processes are reliable, suitable and acceptable.

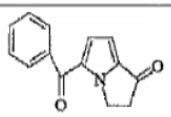
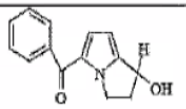
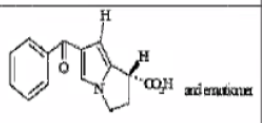
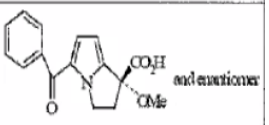
3.2.3 Characterisation (CTD module 3.2.S.3)

Elucidation of structure and other characteristics (CTD section: S.3.1)

Ketorolac tromethamine batch number KTM RS/12 was characterized and confirmed by suitable methods.

Impurities (CTD section: S.3.2)

1. Organic impurities of Ketorolac tromethamine listed in USP monograph

Name of the impurity	Structure
5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-one	
(1RS)-5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-ol	
(1RS)-6-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid	
(1RS)-5-benzoyl-1-methoxy-2, 3-dihydro1H-pyrrolizine-1-carboxylic acid	

2. Additional impurities from API

3. Process related impurities

Assessor's comments on S.3 Characterisation: Documents in this part are acceptable.

3.2.4 Control of drug substance (CTD module 3.2.S.4)

Specification (CTD section: S.4.1)

Ketorolac tromethamine drug substance complies with USP 40 requirements.

Specification of drug substance follows USP 40 and additional on residual solvents. They may occur during in synthetic route of Ketorolac drug substance. Overall, specification is suitable and acceptable.

The applicant attached certificate of analysis of Ketorolac tromethamine consisting of 2 batches, all batches comply with the specification.

Analytical procedure (CTD section: S.4.2)

A valid document is submitted.

Validation of analytical procedure (CTD section: S.4.3)

Method validation of analytical procedures of Ketorolac tromethamine has been performed in order to confirm the analytical procedure using with Ketorolac tromethamine.

Analytical method verification parameters: identification, organic impurities and assay. Analytical method validation parameter: residual solvents (in-house).

The results of validation and verification covered parameters; specificity, precision, accuracy, linearity and robustness.

Batch analyses (CTD section: S.4.4)

The results of analysis met the specifications.

Justification of specification (CTD section: S .4.5)

A document is submitted.

Assessor's comments on S.4 Control of Drug Substance: Specification, analytical method and validation method of drug substance followed USP 40 and in-house standard was also evaluated by method verification and method validation on suitable parameters. In addition, manufacturer tested consistency on 2 batches, the results showed all batches were consistency. They could be summarized that manufacturing process, analytical method, process verification or validation of drug product were reliable, suitable and acceptable.

3.2.5 Reference standards of materials (CTD module 3.2.S.5)

Ketorolac tromethamine (USP) and Ketorolac tromethamine in-house working standard were used. USP certificate and certificate of analysis are also attached.

Assessor's comments on S.5 Reference Standards or Materials: Documents in this section are satisfactory.

3.2.6 Container closure system (CTD module 3.2.S.6)

The container/closure system of Ketorolac tromethamine drug substance is in compliance with requirements.

Assessor's comments on S.6 Container Closure System: Documents in this section are satisfactory.

3.2.7 Stability (CTD module 3.2.S.7)

Stability

Ketorolac tromethamine drug substance is packaged in a clear polythene bag, which was tied and kept in a black polythene bag, then tied and kept in a small HDPE drum, at accelerated condition and long-term condition.

Condition	Number of batches x month	Package
Accelerated condition 40 ± 2°C and 75 ± 5 %RH	3 batches 1, 2, 3 and 6 months.	Proposed package
Long-term condition 25 ± 2°C and 60 ± 5 %RH	3 batches 3, 6, 9, 12, 18, 24, 36, 48, and 60 months.	

The samples are analyzed for the specified stability tests including description, identification, loss on drying, assay, chromatographic purity, microbial test limit and bacterial endotoxins, in long term stability studies.

According to the stability data of Ketorolac tromethamine when stored in such packaging at said conditions, the stability data complies well with the specification. Therefore, we can conclude that the shelf-life of Ketorolac tromethamine drug substance is 60 months (5 years).

Assessor's comments on S.7 Stability: Number of batch, condition, duration and parameters followed by ICH guideline are suitable. The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container.

3.3 Drug product (CTD module 3.2.P)

3.3.1 Description and composition of the drug product (CTD module 3.2.P.1)

Ketromax injection is a colorless to slightly yellow liquid, filled in USP type I colorless and transparent ampoule, together with a plastic ampoule tray and 1 package insert per individual box. One pack size (box) contains 10, 15, 20, 25 or 50 amp/box**.**

Each ampoule (1 mL) contains: Ketorolac tromethamine 30 mg

Packing size: 1 mL per ampoule.

Table: List of components used for Ketromax injection

Name of Material	Function	Reference
Ketorolac Tromethamine	Active ingredient	USP 40
Sodium Chloride	Tonicity agent	USP 40
Ethanol	Co-solvent	In-house
Sodium Hydroxide*	Alkalizing agent	BP 2018
Hydrochloric Acid*	Acidifying agent	BP 2018
Water for injection (add to)	Solvent	USP 40

*Note: These ingredients are used to adjust the pH only.

3.3.2 Manufacture (CTD module 3.2.P.3)

Manufacturer(s) (CTD section: P.3.1)

Finished product manufacturing site	Responsibility
Siu Guan Chem. Ind. Co., Ltd. No. 128, Shinmin Road, Hunei Village, West District, Chiayi City, Taiwan, R.O.C.	- Manufacturing - Packaging - Quality control testing and releasing

Batch formulation (CTD section: P.3.2)

Batch size of Ketorolac tromethamine is also proposed as a commercial batch.

Manufacturing process and in-process control

The manufacturing process and in process control of Ketorolac tromethamine drug product was described.

Controls of Critical Steps and Intermediates

The controls of critical steps were described.

Process validation

Process validation of Ketromax injection had been performed with 3 production batches. Based on all available data, three batches of Ketromax injection met the requirements for all process validation specifications.

Furthermore, according to the sterilization process validation, all tracking parameters are well complying with the requirements.

So, Ketromax injection is well complying with the process validation and sterilization process validation.

Assessor's comments on P.3 Manufacture: Siu Guan Chem. Ind. Co., Ltd. is suitable and acceptable manufacturer. They show valid certificate of GMP compliance of manufacturer from competent authority of Taiwan (Republic of China). The process is considered to be a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable for producing the finished product of intended quality in a reproducible manner.

The formulation including active ingredient and excipients complies with USP 40, BP 2018 and in-house specification, showing that formulation has standard and acceptable. Moreover, there is no novel excipients in the formulation.

3.3.3 Control of excipients (CTD module 3.2.P.4)

Control of excipients

Analytical procedures of sodium chloride, ethanol, sodium hydroxide, hydrochloric acid and water for injection, are well complying with the reference (USP 40 and BP 2018). There was no ingredients from human or animal origin and novel excipients.

Assessor's comments on P.4 Control of excipients: Documents in this section are satisfactory.

3.3.4 Control of drug product

Product specification

The specification of drug product was performed under the compliance with USP 40.

Validation of analytical procedures

Analytical method validation (assay, sterility and organic impurities), all of them were conducted by acceptable standard.

Batch analysis

Three batches of Ketromax injection were analyzed in compliance with USP 40 for batch analysis. All batches met the acceptance criteria.

Assessor's comments on P.5 Control of drug product: There are specification, analytical method and validation of analytical method. All of them were conducted by acceptable standard. Manufacturing process of drug product, follows USP 40, is verified by analytical method validation. Moreover, manufacturer identify an in process control in each steps for consistency. Overall, we can summarise that manufacturing process of drug product is suitable, reliable, consistent and acceptable.

3.3.5 Reference standard or materials

Assessor's comments on P.6 Reference standards or materials: Documents in this section are satisfactory.

3.3.6 Container closure system

Ketromax injection is packaged in USP Type I colorless and transparent ampoule containing 1 mL of injection. 10, 15, 20, 25, and 50 ampoules are packed in a paper box together with a plastic ampoule tray and a package insert.

Primary packaging materials	1. USP Type I colorless and transparent ampoule
Secondary packaging materials	1. Plastic ampoule tray 2. Paper box 3. Package insert

Assessor's comments on P.7 Container closure system: Information in this section demonstrates adequate standard of the container closure system.

3.3.7 Stability of the product

On the basis of the accelerated stability test data (40°C ± 2°C, 75 ± 5% RH) and long-term stability test data (30°C ± 2°C, 75 ± 5% RH), it is concluded that Ketromax injection has tentative shelf-life to be stable for 24 months at the storage temperature below 30°C, as recommended by ASEAN guideline for drug product stability study. The specifications for stability testing were as same as release specifications.

Conclusion of stability study

According to the stability data of Ketromax injection, which studied in the accelerated

condition (40°C ± 2°C, 75 ± 5% RH) for 6 months and long-term condition (30°C ± 2°C, 75 ± 5% RH) for 12 months, it has shown that all three batches of Ketromax injection were stable in all aspects and complying with the USP 40 requirements. There were no significant change in physical, chemical, and biological stability under said conditions for all along the study period. Therefore, it can be concluded that Ketromax injection is stable for at least 6 months under the accelerated condition (40°C ± 2°C, 75 ± 5% RH) and stable at least 12 months under the long-term condition (30°C ± 2°C, 75 ± 5% RH). So, declaring that Ketromax injection has the tentative shelf-life for 24 months.

Assessor's comments on P.8 Stability: Documents in this section are satisfactory.

4. Assessor's overall conclusions on quality

Quality aspect of this product is considered to be satisfactory.

Assessor's comments on the SmPC, labelling and package leaflet

SmPC

The SmPC contains all necessary information and meets the Thai FDA requirements. Therefore, it is considered to be satisfactory.

Labelling

The data in unit carton from American Taiwan Biopharm Co., Ltd. meets the criteria for readability as set out in the standard of Thai FDA 2009; Guideline for Leaflet Development and ASEAN Harmonization.

Unit carton

No.	Topic	Yes	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of active ingredients	✓	✓
4	Strength of active ingredients	✓	✓
5	Batch number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of administration	✓	✓
9	Storage condition	✓	✓
10	Country's registration number	✓	✓
11	Name and address of marketing authorization holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labelling	✓	✓

14	Recommended daily allowance (vitamins and minerals)	n/a	n/a
15	Warning (as indicated by ministerial announcement)	n/a	n/a
16	Pack sizes	✓	✓

✓ Suitable data

n/a not applicable

Inner Label (ampoule area < 3 inches^2)

No.	Topic	Yes	Appropriate
1	Product name	✓	✓
2	Name of active ingredients	✓	✓
3	Strength of active ingredients	✓	✓
4	Batch Number	✓	✓
5	Expiration date	✓	✓
6	Route of Administration	✓	✓
7	Pack sizes	✓	✓

✓ Suitable data

n/a not applicable

Assessor's comments on Patient Information Leaflet (PIL)

Patient Information Leaflet (PIL) is suitable, complete, and in accordance with the SmPC. As part of post-marketing risk management plan, data is presented by summarizing the easy-to-understand key important points that patients should follow in taking this drug.

5. Overall Benefit/risk assessment

According to the data submitted to support the quality of Ketromax injection, the manufacturing process, analytical method and quality control are suitable. It can be concluded that quality of Ketromax is acceptable and meets the standard criteria. Registering indication is consistency with original product, Ketolac®, approved in Thailand. Its indication "Ketorolac injection is indicated for the short-term management of moderate to severe acute post-operative pain. Treatment should only be initiated in hospitals. The maximum duration of treatment is 5 days." is appropriate.

Ketromax is registered as a generic medicinal product without bioequivalent. However, the original product, Ketolac®, is a special-controlled medicine. So, MAH has to follow up the safety monitoring program and comply it with the protocol. Ketromax will be approved as a special-controlled medicine, and the overall benefit/risk assessment supports approval of Ketromax, are including the following 4 requirements;

1) Utilized in the hospital (โรงพยาบาล) and specified on the label.

2) Follow up the adverse event in post-marketing in accordance with SMP protocol submitted in section 1.8.3, SMP protocol in eCTD.

3) Perform PIL usability testing within 12 months after authorization and report to Thai FDA.

4) Submit long-term stability report in proposed condition and duration for supporting shelf-life approval.

Appendix 1
(Labelling)

Labelling of carton

Labelling of ampoule