Date: December 6, 2019

Division of Dockets Management
U.S. Food and Drug Administration Department of Health and
Human Services Room 1061, l-IFA-305
5630 Fishers Lane
Rockville, MD 20852

ANDA Suitability Petition for new drug combination of Chlorzoxazone and Acetaminophen Tablets, 250 mg/300 mg

Dear Sir/Madam,

Pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act), and in accordance with 21 C.F.R. § 10.20, 10.30 and 314.93, Aavis Pharmaceuticals, submits this ANDA Suitability Petition. The Suitability Petition requests that the FDA determine that new drug combination of Chlorzoxazone and Acetaminophen in tablets dosage form is suitable for submission in an Abbreviated New Drug Application (ANDA).

A. Action Requested:

The Suitability Petition requests that the FDA determine that the proposed new drug combination of Chlorzoxazone and Acetaminophen Tablets is suitable for submission in an ANDA. This Suitability Petition pursuant to MAPP 5240.5 Rev. 1, 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 new drug combination of Chlorzoxazone and Acetaminophen Tablets.

B. Statement of Grounds:

The FDC Act permits, at Section 505(j)(2)(A)(iii) and 21C.F.R. §314.93, the submission of an ANDA for a drug product is a combination product with one different active ingredient after FDA has approved a petition seeking permission to file such an application. Several prescription and OTC products for fixed dose combination with acetaminophen and individual drug product for acetaminophen and chlozoxazone is approved in the USA. List of the approved product is attached as **Annex-1**.

However the combination of Chlorzoxazone and Acetaminophen is not approved in USA. The combination of Chlorzoxazone and Acetaminophen Tablets is approved in Canada as an OTC product. The prescribing information of the same is provided as **Annex-II**.

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal conditions. Data available from animal experiments, as well as human study, indicate that chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology. The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles. Blood levels of chlorzoxazone can be detected in humans during the first 30

minutes after oral administration and peak levels may be reached in about 1 to 2 hours. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than 1% of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

Acetaminophen provides analgesic action to supplement that which results secondarily from muscle relaxation. Acetaminophen is rapidly absorbed after oral administration, with peak plasma levels occurring in 1 to 2 hours. After 8 hours, only negligible amounts remain in the blood. Only 4% is excreted unchanged; 85% of the ingested dose is recovered in the urine in conjugated form as the glucuronide. Acetaminophen is distributed throughout most tissues of the body. Acetaminophen is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

Chlorzoxazone is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.

Musculoskeletal pain is caused by an injury to the bones, joints, muscles, tendons, ligaments, or nerves. This can be caused by jerking movements, car accidents, falls, fractures, sprains, dislocations, and direct blows to the muscle. Musculoskeletal pain can also be caused by overuse.

Acetaminophen is indicated for temporarily relieves minor aches and pains and also act as anti-inflammatory.

Chlorzoxazone with Acetaminophen will give synergic effect and improve the pain relief result. Based on the information available no drug-drug interaction found between chlorzoxazone and acetaminophen

Considering the information provided in FDA database and in literature the maximum daily dose of Chlorzozone is 3000 mg and for Actaminophne is 4000 mg. However based on the information provided in Health Canada prescription information leaflet we wish to propose following dose

DOSAGE AND ADMINISTRATION
Adults: (12 years of age and older) 2 tablets 4 times a day. It is hazardous to exceed 8 tablets per day. For more information please refer draft prescribing information attached as **Annex-III.**

OTC monograph of Acetaminophen is available and in most of the product specific guidance Acetaminophen is rated as “AA” drug. Chlorzoxazone is also rated “AA” in orange book and product specific guidance of 250 mg tablets. Product specific guidance attached as **Annex-IV**.

Considering this the new combination of Chlorzoxazone and Acetaminophen Tablets 250 mg; 300 mg should also be eligible for complete bio-waiver.

C. Environmental Impact:

Aavis claims a categorical exclusion under 21 C.F.R. § 25.31.

D. Economic Impact Statement:

Aavis does not believe that this requirement is applicable at this time, but will agree to submit economic impact information, in accordance with 21 C.F.R. § 10.30(b), if requested by the Agency.

E. Certification:

Aavis 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:

During the course of the review of this application, if there are any questions or comments, please do not hesitate to contact undersigned via telephone at +1-706-684-0388, facsimile at +1-706-684-0393 or e-mail: dbarot@aavispharma.com.

Sincerely,

Digitally signed by
DHANANJAY BAROT
Date: 2019.12.06
04:30:26 -05'00'

Dhananjay Barot
President
Aavis Pharmaceuticals.

Enclosure:

1. List of the approved product (Annex-I)
2. Prescribing information of Canada approved product (Annex-II)
3. Draft prescribing information (Annex-III)
4. Product specific guidance (Annex-IV)