



ANDA XXXXXX

SUPPLEMENT REQUEST

[Sponsor Contact]

Dear [Sponsor Representative]:

Please refer to your abbreviated new drug application (ANDA) for [Insert Tradename] (Insert established name) [capsules/tablets, strength].

SAFETY LABELING CHANGES

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Section 505(o)(4) also authorizes FDA to require the holder of an approved application under section 505(j) (an ANDA) to make safety related label changes based upon new safety information if the same drug approved under section 505(b) is not currently marketed. You are the holder of ANDA XXXXXX which references a drug approved under section 505(b) that is not withdrawn and not currently marketed.

Since [Insert Tradename] was approved on [Insert year of approval], we have become aware of postmarketing adverse event reports describing serious cardiovascular adverse reactions, including death, associated with the use of oral terbutaline sulfate for prolonged tocolysis (beyond 48-72 hours). We have also become aware of animal studies, published in peer-reviewed biomedical literature, in which the offspring of rat dams treated with terbutaline sulfate during the late stage of pregnancy and the lactation period exhibited alterations in behavior and brain development. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for all oral formulations of terbutaline sulfate as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

Add a **BOXED WARNING** to the package insert as described below:

WARNING: TOCOLYSIS

Oral terbutaline sulfate has not been approved and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for maintenance tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See Contraindications, Tocolysis.]

Revise the **CONTRAINDICATIONS** section of the package insert as described below:

CONTRAINDICATIONS

1. Tocolysis

Oral terbutaline sulfate has not been approved and should not be used for acute or maintenance tocolysis. [See *Boxed Warning: Tocolysis*.]

2. Hypersensitivity

Terbutaline sulfate is contraindicated in patients known to be hypersensitive to sympathomimetic amines or any component of this drug product.

Revise the *Tocolysis* and *Pregnancy-Teratogenic Effects* subsections of the **PRECAUTIONS** section of the package insert as described below:

PRECAUTIONS

Tocolysis

~~Terbutaline sulfate has not been approved and should not be used for tocolysis. Serious adverse reactions may occur after administration of terbutaline sulfate to women in labor. In the mother, these include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.~~

Pregnancy - Teratogenic Effects

~~Pregnancy Category **B** C~~

~~A reproduction study in Sprague-Dawley rats revealed terbutaline sulfate was not teratogenic when administered at oral doses of 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m² basis). A reproduction study in New Zealand white rabbits revealed terbutaline sulfate was not teratogenic when administered at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily oral dose for adults on a mg/m² basis).~~

There are ~~however~~, no adequate and well-controlled studies of terbutaline sulfate in pregnant women. Published animal studies show that rat offspring exhibit alterations in behavior and brain development, including decreased cellular proliferation and differentiation when dams were treated subcutaneously with terbutaline during the late stage of pregnancy and lactation period. Terbutaline exposures in rat dams were approximately 6.5 times the common human dose in adults of 15 mg/day, on a mg/m² basis.

Oral terbutaline sulfate has not been approved and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See *Boxed Warning: Tocolysis and Contraindications, Tocolysis.*]

In animal embryofetal developmental studies, no teratogenic effects were observed in offspring when pregnant rats and rabbits received terbutaline sulfate at oral doses up to 50 mg/kg/day, approximately 32 and 65 times, respectively, the maximum recommended daily oral dose for adults, on a mg/m² basis.

Because animal reproduction studies are not always predictive of human responses, this ~~drug~~ Terbutaline sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See PRECAUTIONS, Tocolysis).

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

If you are the holder of a product approved under 505(j), and are currently listed in the discontinued section of the Approved Drug Products with Therapeutic Equivalence “Orange Book”, you have 30 days in which to submit any objections to the above safety labeling changes, or draft labeling with the requested updates.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(O)(4)-AMENDMENT**

To facilitate review of your submission, please provide a side-by-side comparison of your proposed labeling and the labeling of the reference listed drug with all differences annotated and explained. Include labeling in Final Printed Labeling (FPL) and Microsoft Word format.

If you have any questions, please contact Jeanne Skanchy, Labeling Reviewer, at jeanne.skanchy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kieth Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research