MEMORANDUM

DATE: 22 March 2019

TO: Cipla USA's ANDA for ambrisentan tablet (ANDA 210715)

Zydus Pharmaceuticals (USA) Inc.'s ANDA for ambrisentan tablet (ANDA 210058)

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SUBJECT: Decision to waive the requirement for a single, shared system REMS program for ambrisentan tablet products

This memorandum explains the Food and Drug Administration's (FDA's or the Agency's) decision to waive the requirement for a single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for the ambrisentan tablet products listed above. Zydus Pharmaceuticals (USA) Inc. (Zydus) and Cipla USA (Cipla) have filed abbreviated new drug applications (ANDAs) to market generic versions of Letairis (ambrisentan) tablets – a product marketed under a new drug application (NDA) held by Gilead Sciences, Inc. (Gilead) (NDA 22081), as the reference listed drug (RLD). Letairis is approved with a REMS that includes elements to assure safe use (ETASU).

Section 505-1(i)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a generic drug (e.g., ambrisentan) is subject to certain elements of the REMS required for the applicable listed drug (e.g., Letairis), including elements to assure safe use, and requires that the generic drug and the applicable listed drug use a SSS for the ETASU. It also gives FDA the authority to waive this requirement if the Agency determines that the burden of creating a SSS outweighs its benefits, taking into account the impact on certain stakeholders, or if an ANDA applicant certifies that it sought a license for use of an aspect of the applicable listed drug's

ETASU claimed by a patent that has not expired or a method or process that, as a trade secret, is entitled to protection, and was unable to obtain one.

As explained in more detail below, FDA finds that the standard for granting a waiver of the SSS REMS requirement has been met with respect to the ANDAs listed above, because the burden for these applicants of joining a SSS REMS with the RLD outweighs the benefits. Accordingly, the Agency waives the SSS REMS requirement for these products.

To help ensure that this decision does not unduly burden health care providers, patients, or the U.S. healthcare system in general, FDA is attaching a condition to the waiver: that this waiver-granted REM be open to all current and future applicants with ambrisentan products that reference Letairis.

I. BACKGROUND

Letairis (ambrisentan) was initially approved on June 15, 2007. It is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Letairis was initially approved with restrictions to assure safe use under the provisions of the Subpart H regulations (21 CFR 314.520). Under section 909(b)(1) of the Food and Drug Administration Amendments Act (FDAAA), the Agency identified Letairis as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520. (See 73 Fed. Reg. 16313 (Mar. 27, 2008)). The Letairis REMS was approved on May 29, 2009.

FDA also is approving a modified REMS for Letairis, which includes a SSS with Gilead, called the Ambrisentan REMS. For purposes of this memorandum, this REMS is also referred to as the RLD REMS.

a. The RLD REMS[1]

The goal of the RLD REMS is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

1. Ensuring prescribers are educated on the following:
    - the risk of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
    - counseling patients about the risk and the need for monthly monitoring
    - enrolling patients in the Ambrisentan REMS Program
    - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
    - the risk of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
    - confirming that the appropriate patient monitoring and counseling has occurred before dispensing ambrisentan
5. Ensuring that patients are informed about:
    - the risk of embryo-fetal toxicity
    - appropriate baseline and monthly patient monitoring
      appropriate contraception

The RLD REMS consists of several ETASU, which require:

1. Healthcare providers who prescribe ambrisentan are specially certified. To become certified, prescribers agree, on the *Prescriber Enrollment and Agreement Form*, that they have read the prescribing information (PI) and the *Prescriber Guide* and they understand the requirements of the program. Furthermore, certified prescribers agree to counsel and enroll all female patients in the REMS Program.

2. Pharmacies, practitioners and healthcare settings that dispense ambrisentan are specially certified. To become certified, all pharmacies and healthcare providers (HCP) (i.e. practitioners) who dispense ambrisentan agree, on the appropriate *Pharmacy Enrollment Form*, that the authorized representative has reviewed the *Pharmacy Guide* and they understand the requirements of the program. Furthermore, they will ensure the certified pharmacy or HCP only dispense ambrisentan pursuant to a prescription from a certified prescriber to enrolled patients or patients who will be enrolled prior to discharge from an inpatient facility.

[1] See section 505-1 of the FD&C Act. The currently approved RLD REMS can be found on the FDA's Approved REMS website: http://www.accessdata fda.gov/scripts/cder/rems/index.cfm

3. Ambrisentan will be dispensed to female patients with evidence or other documentation of safe-use conditions. A certified prescriber will enroll all female patients in the Ambrisentan REMS program by counselling the patient and completing the *Patient Enrollment Form*. Certified pharmacies and HCPs will only dispense ambrisentan pursuant to a prescription from a certified prescriber to female patients after ensuring the patient is enrolled or will be enrolled prior to discharge from an impatient facility (i.e. the documentation of safe-use condition is complete)

Finally, the RLD REMS includes an implementation system through which the applicants evaluate and monitor compliance with the REMS requirements, as well as a timetable for the submission of REMS assessments.

a. Statutory Standard

The Agency's authority to waive the requirement for a SSS REMS is governed by Section 505-1(i)(1)(C) of the FD&C Act. In relevant part, Section 505-1(i)(1)(C) states:

> The Secretary may waive the [SSS REMS requirement] for a drug that is the subject of an abbreviated new drug application, and permit the applicant to use a different, comparable aspect of the elements to assure safe use, if the Secretary determines that—
>
> (i) the burden of creating a single, shared system outweighs the benefit of a single system, taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product. . . .[2]

Thus, FDA may waive the requirement that the RLD and any approved ANDA that references the RLD use a SSS REMS, provided the Agency determines (1) that the generic drug's REMS uses aspects of the ETASU that are "comparable" to those of the RLD's REMS, and (2) that the burden of creating a SSS REMS outweighs the benefit of such a SSS REMS, taking into account the impact on the statutorily-identified stakeholders.

b. Negotiations for a SSS REMS for Ambrisentan

On July 27, 2015, FDA met with RLD applicant Gilead and ANDA applicants Actavis Laboratories FL, Inc. (Actavis) and Sigmapharm Laboratories, LLC (Sigmapharm) to discuss the Agency's expectations for development of a SSS REMS for ambrisentan tablets pursuant to

[2] As noted above, the statute also permits FDA to grant a waiver in situations where the ANDA applicant has been unable to obtain a license to a protected aspect of the listed drug's REMS. Section 505-1(i)(1)(C)(ii). That provision does not apply here, as the inability to obtain a license to an aspect of Gilead, Inc.'s REMS is not at issue.

Section 505-1 of the FD&C Act.[3] To facilitate the timely development of a SSS REMS for ambrisentan, FDA recommended timeframes within which the parties should achieve certain milestones. The timeframes recommended by the Agency were as follows:

- 30 days following the meeting the applicants should have a signed confidentiality and disclosure agreement governing their negotiations for a SSS REMS for ambrisentan.
- 120 days following the meeting the applicants should have agreed on governance document defining cost sharing and other terms.
- 165 days following the meeting the applicants should each submit a copy of the shared REMS document to the FDA for review and approval.

Six more ANDAs were received following the meeting, and the Agency communicated the relevant information to those applicants as well. The Agency requested the parties submit joint biweekly updates on the status of the negotiations and program development.

On January 19, 2016, three ANDA applicants submitted a separate bi-weekly update stating that they had formed a separate industry working group called the Ambrisentan ANDA REMS Group (AARG) and stating their intention to develop a separate REMS due to an impasse in negotiations with the RLD applicant, Gilead. The AARG described the situation as follows:

> The Industry Working Group[4] legal subteam, met to discuss remaining Memorandum of Understanding (MOU) differences on January 14, 2016. Members of the operations subteam were present on the teleconference. During the course of the meeting, two major concerns were discussed: first, unanimous versus majority rule for vendor selection, and second, the restricted distribution of ambrisentan through the exclusive use of specialty pharmacies.
>
> The RLD Sponsor (Gilead) rejected the ANDA sponsors' proposal to include all pharmacies willing to meet REMS certification requirements under the shared REMS program. The RLD Sponsor firmly maintained the view that ambrisentan should solely be available through the use of specialty pharmacies. Thus, a mutually agreeable solution could not be attained. Consequently, Gilead suggested that the ANDA sponsors seek a waiver request.[5]

[3] At the time, only two ANDAs referencing Letairis as the RLD had been received by the Agency: Actavis's (formerly Watson Laboratories, Inc.'s) ANDA 208252 and Sigmapharm's ANDA 208354.

[4] At this time, the Industry Working Group included Mylan Pharmaceuticals Inc., Sigmapharm Laboratories, LLC, Watson Laboratories, Inc. (now Actavis Laboratories FL, Inc.) and Gilead Sciences, Inc.

[5] See, e.g., ANDA 208252, Sequence 0017 (Jan. 19, 2016).

On February 11, 2016, Gilead submitted a REMS Correspondence with the stated purpose of providing additional context regarding the circumstances giving rise to the impasse in negotiations regarding the SSS REMS for ambrisentan. Gilead states that it "does not oppose FDA granting a waiver of the requirement for a single shared [system] REMS for ambrisentan under the provisions in section 505-1(i) of the Federal Food, Drug, and Cosmetic Act (FDACA); provided that any separate REMS approved for an ANDA complies with all the requirements of the FDACA, including the requirement that any separate REMS for an ANDA that references Letairis includes comparable aspects of the same elements to assure safe use required in the Letairis REMS."

On June 6, 2016, the AARG submitted a proposed REMS document for a separate, waiver-granted REMS. Amendments with revised REMS documents were submitted on August 8, 2017, December 7, 2017, June 22, 2018, and August 31, 2018.

On December 7, 2017, Zydus submitted a request for the Agency to grant a waiver.

On March 6, 2018, Cipla submitted a request for the Agency to grant a waiver.

On June 22, 2018, Zydus and Cipla submitted a revised waiver request to update membership in the AARG.

On November 23, 2018, Cipla submitted an updated request for the Agency to grant a waiver.

II. ANALYSIS

In June 2018, FDA issued a draft guidance for industry entitled, *Waivers of the Single, Shared System REMS Requirement*,[6] in which the Agency describes the factors FDA will consider in evaluating a request for a waiver of the SSS requirement. The guidance explains that the Agency will do a case-by-case analysis to determine whether the statutory criteria have been met. In this case there are no aspects of the ETASU in the RLD REMS that are protected by patent or exclusivity. The necessary determination, therefore, is whether the burden of forming a SSS REMS outweighs the benefits, taking into consideration the impact on patients, health care providers, and the RLD holder and ANDA applicants.

FDA has determined that the burden of forming a SSS REMS for the ambrisentan products listed above outweighs the benefits of a SSS system, as described below. Zydus and Cipla submitted a proposed REMS, separate from the RLD REMS, that has the same goals and uses comparable

[6] Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm609048.pdf

aspects of the ETASU. Therefore, a waiver of the SSS requirement in this case is appropriate under the legal standard for granting a waiver.

a. The Burden of Creating a Single, Shared System Outweighs the Benefits

In accordance with section 505-1(i)(1)(C) of the FD&C Act, the Agency has considered the effects of granting a waiver and permitting a second, separate REMS for some ambrisentan products on health care providers, patients, the ANDA applicants, and the RLD holder. The Agency concludes that, on balance, the impacts on these stakeholders favor granting a waiver.

Based on our experience, the formation of a SSS between an RLD holder and ANDA applicants can be a complex and time-consuming process. Development of a SSS REMS is dependent on negotiations and establishment of agreements between companies, as well as completion of numerous steps to develop and manage a shared program. These negotiations must be carried out between companies that are marketplace competitors. In this case, the parties negotiated for several months but were unable to agree on central threshold issues necessary to proceed with development of a SSS REMS. In particular, these ANDA applicants were interested in utilizing retail pharmacies for distribution of ambrisentan products, while the RLD remained committed to using solely specialty pharmacies.

While a SSS would provide benefits to stakeholders by avoiding the potential confusion and inefficiency associated with the existence of two REMS for ambrisentan, these benefits do not outweigh the burdens of (1) the time and resources expended by the AARG applicants and the RLD to create a SSS REMS, (2) a delay in the approval of additional safe and effective generic ambrisentan alternatives, and (3) limiting access to generic ambrisentan by preventing its dispensing by retail pharmacies. The Agency's findings with respect to the impacts on each stakeholder group are summarized below.

1. Health Care Providers

The existence of two REMS will create some inefficiencies for prescribers and some pharmacies. Both REMS require that prescribers and pharmacies be certified in the REMS program. Therefore, prescribers who want to prescribe both Letairis and generic products that are in the waiver-granted REMS will have to certify in both programs. Prescribers will also have to enroll some patients in both programs if they switch between a product in the RLD REMS and a product in the waiver-granted REMS for any reason, including because the patient chooses to use retail pharmacies or due to insurance provider preferences. Likewise, inpatient and outpatient specialty pharmacies will have to certify in two separate REMS programs if they dispense both Letairis and generic products that are in the waiver-granted REMS. Outpatient retail pharmacies will not be impacted since the RLD REMS will be limited to specialty outpatient pharmacies. Both prescribers and applicable pharmacies need only complete the additional certification once.

FDA believes the burden of these one-time duplicate certifications is outweighed by the burden associated with the delay in availability of additional generic ambrisentan tablet products and the limitation on access to generic drugs posed by preventing dispensing by retail pharmacies.

2. Patients

The Agency finds that a waiver will benefit patients. The primary benefit for patients is that the waiver-granted system will permit patient access to additional generic ambrisentan products. If FDA waits to approve Zydus' or Cipla's pending ambrisentan ANDA until the parties reach agreement on a SSS REMS, patients will be deprived of access to additional generic ambrisentan products for an indefinite period of time. Additionally, since the waiver-granted REMS will allow dispensing by retail pharmacies, patients will have more options for where and how to fill their prescriptions.

Patients may have to be enrolled in two separate REMS programs if they switch between a product in the RLD REMS and a product in the waiver-granted REMS for any reason, including because they choose to use retail pharmacies or due to insurance provider preferences. However, that additional step need only be completed once. FDA believes the burden associated with these duplicate enrollments is outweighed by the burden associated with the delay in availability of one or more generic ambrisentan tablet products and the prevention of dispensing by retail pharmacies.

3. ANDA Applicants

Absent a waiver, approval of Zydus' or Cipla's pending ANDA will be delayed until the parties reach an agreement on a SSS REMS. By granting a waiver, the Agency will remove a barrier to these generic products coming to market. The Agency's decision to grant a waiver will benefit Zydus and Cipla and future ANDA applicants to the extent it will allow ANDA applications that otherwise meet the statutory standard to be approved, the result intended by the Hatch-Waxman amendments. The burden of SSS development outweighs any potential benefit to ANDA applicants from such a system.

4. RLD Applicant

We do not believe that granting a waiver would impose a burden on the RLD applicant, Gilead. A waiver does not affect Gilead's ability to continue using its approved REMS, nor does it affect the cost of that REMS. In addition, Gilead explicitly stated that it did not oppose the granting of a waiver to the ANDA applicants, provided that their separate REMS satisfied the statutory requirements for approval.

b. Zydus' and Cipla's proposed REMS is comparable to the approved REMS for Letairis

Section 505-1(i)(1)(C) of the FD&C Act provides that an ANDA is subject to the ETASU for the RLD, but if FDA waives the requirement to use a SSS, FDA may permit ANDA applicants to use a "different, comparable aspect of the [ETASU]." FDA interprets this standard to mean that a waiver-granted system for ETASU must include the same ETASU as described in the statute. For example, if the RLD's ETASU consist of prescriber certification (under 505-1(f)(3)(A)) and dispensing of a drug only in certain healthcare settings (under 505-1(f)(3)(C)), the ANDA system must include those elements as well. FDA further interprets "different, comparable aspect of the [ETASU]" to allow a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirement, provided the program achieves the same level of safety.

Zydus and Cipla submitted a proposed separate REMS for their ambrisentan ANDAs that closely mirrors the RLD REMS. The proposed REMS has the same goals and the same ETASU (prescriber certification, pharmacy certification, and documentation of safe use conditions) as those of the RLD REMS. The proposed REMS achieves the same level of safety as the RLD REMS despite the operational differences.

Prescriber Certification

Both the RLD REMS and the waiver-granted REMS require prescriber certification (ETASU A) and operationalize the requirement identically. Both REMS require that prescribers review the Prescribing Information and the REMS educational materials and agree to assess reproductive and pregnancy status of each female patient, enroll each female patient in the REMS program, counsel females of reproductive potential (FRP) and pre-pubertal female patients, and report pregnancies. Prescribers certify in the program by completing and submitting the *Prescriber Enrollment Form* which can be accomplished in multiple ways (e.g. on websites, fax) and formats (e.g. electronic, print). The REMS educational materials for prescribers contain the same information about the risks the REMS is intended to mitigate.

Pharmacy Certification

Both the RLD REMS and the waiver-granted REMS require pharmacy certification (ETASU B). Both REMS require that all pharmacies and healthcare providers who dispense ambrisentan tablets certify in the REMS program in order to dispense the products.

<u>Outpatient Pharmacies and healthcare providers who dispense</u>

Under both REMS, outpatient pharmacies and healthcare providers who dispense must become certified. They must agree to designate an authorized representative to enroll in the REMS by completing the *Outpatient Pharmacy Enrollment Form* and submitting the form to the appropriate REMS Coordinating Center. The authorized representative will oversee implementation and compliance with the REMS on behalf of the pharmacy and ensure that all

pharmacy staff involved in the dispensing of ambrisentan are trained using the Pharmacy Guide. The pharmacy is required to re-certify if the pharmacy designates a new authorized representative.

In both programs, prior to dispensing ambrisentan, outpatient pharmacies and healthcare providers who dispense ambrisentan tablets must verify that the prescriber is certified, the female patient is enrolled, and the FRP has had a pregnancy test and is counseled on the safe use of ambrisentan. Other certification requirements include reporting pregnancies, changes in reproductive status, or misclassifications of reproductive status to the REMS Program, not distributing or transferring ambrisentan except to certified dispensers, compliance with audits, and maintaining records that all processes and procedures are in place and are being followed.

These dispensing requirements are identical but operationalized differently in the RLD REMS and the waiver-granted REMS. In the RLD REMS, the outpatient pharmacy performs the required verifications through communication with the RLD REMS coordinating center. The outpatient pharmacy is responsible for contacting the FRP monthly to obtain confirmation of pregnancy testing or contacting the prescriber to authorize the refill. The outpatient pharmacy is also responsible for counseling the FRP. In the waiver-granted REMS, some of these responsibilities are shifted from the outpatient pharmacies to a central REMS coordinating center. The outpatient pharmacies perform the necessary verifications by obtaining a REMS Dispense Authorization (RDA) from the waiver-granted REMS coordinating center. The REMS coordinating center provides an RDA to the outpatient pharmacy only if the prescriber is certified, the female patient is enrolled, the female patient's reproductive status has not changed, and, for FRP, a pregnancy test was completed or the prescriber authorized the refill. The RDA from the coordinating center also provides the outpatient pharmacy with the status of monthly FRP patient counseling. In cases where the FRP has not been counseled by the REMS coordinating center, the RDA contains a warning message that alerts the pharmacist to direct the FRP to contact the REMS coordinating center or elect to use counseling guidelines to conduct the counseling with the patient. If the pharmacy counsels the FRP, it is to be documented and provided to the REMS coordinating center.

These operational differences are necessary to accommodate the different types of outpatient pharmacies (including retail and specialty pharmacies) used by the two programs. Counseling patients about their medications and confirming safe use conditions such as pregnancy testing has been routinely incorporated into the workflow of specialty pharmacies. Not all retail pharmacies have the time and resources needed to confirm safe use conditions. By shifting some of the requirements from the pharmacies to a central coordinating center, the waiver-granted REMS would enable retail pharmacies to dispense ambrisentan safely. Importantly, the same safe use conditions are met despite different operational means. FDA finds these operational changes to be acceptable and has determined that, as designed, the waiver-granted REMS will achieve the same level of safety as the RLD REMS.

Inpatient Pharmacies

In the inpatient setting, both REMS require that ambrisentan be dispensed to female patients only after the pharmacy verifies the female patient is enrolled or will be enrolled in the REMS program prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified prescriber. For FRP's, the pharmacy verifies pregnancy testing is complete and that the patient has been counseled on risk of embryo-fetal toxicity, the need to use contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately. Upon discharge, no more than a 15 days' supply will be dispensed.

Documentation of Safe Use Conditions

Both the RLD REMS and the waiver-granted REMS require documentation of safe use conditions (ETASU D) and operationalize this requirement identically. Both programs require all female patients be enrolled in the REMS by a certified prescriber. Patients are enrolled when a prescriber completes the *Patient Enrollment Form* and submits the form to the appropriate REMS Program. By signing the *Patient Enrollment Form*, the female patient acknowledges that she has read the *Patient Guide*. Additionally, FRPs agree to be contacted by the REMS Program prior to each ambrisentan fill to obtain confirmation that pregnancy testing was completed, to be counseled monthly on the requirements of the ambrisentan REMS program and the risks of ambrisentan, and to be contacted by the REMS Program if she becomes pregnant while on ambrisentan or within 30 days after treatment discontinuation. Pre-pubertal females are evaluated annually to determine if there has been a change in reproductive status.

Conclusion

As required by Section 505-1(i)(1)(C), the waiver-granted REMS program will have elements to assure safe use that are comparable to those in the RLD REMS. Specifically, both programs require prescriber certification addressing the same information regarding the risks of ambrisentan and will require prescribers to enroll all female patients. In addition, FRP must verify their pregnancy testing has been completed prior to being dispensed ambrisentan. Pharmacies will be required to certify in the program in order to dispense the products and can only dispense the products after verifying the safe use conditions are met. Finally, both programs require all female patients be enrolled in the REMS and that these patients receive the same safety information about ambrisentan when they are enrolled in the REMS as a documentation of safe use conditions. The operational differences between the REMS programs are acceptable and this REMS will achieve the same level of safety as the RLD REMS.

c. A Conditional Waiver is Appropriate

FDA is attaching the following condition to the waiver: the waiver-granted REMS shall be open to all current and future applicants with ambrisentan products that reference Letairis. The

primary purpose of this condition is seeking to minimize the number of ETASU systems with which stakeholders would need to comply.[7] FDA will closely monitor compliance with this condition and take appropriate action if there is credible evidence that any future ANDA applicant is being refused entry into this waiver-granted REMS.

V. Conclusion

For the foregoing reasons, FDA has decided to waive the requirement that ambrisentan tablet products use a SSS REMS. The waiver shall be conditioned on a requirement that Zydus and/or Cipla make its REMS open to all current and future applicants with ambrisentan tablet products.

[7] FDA has imposed the same condition in all three other waivers of the SSS requirement: buprenorphine, alosetron, and sodium oxybate.

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/s/

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