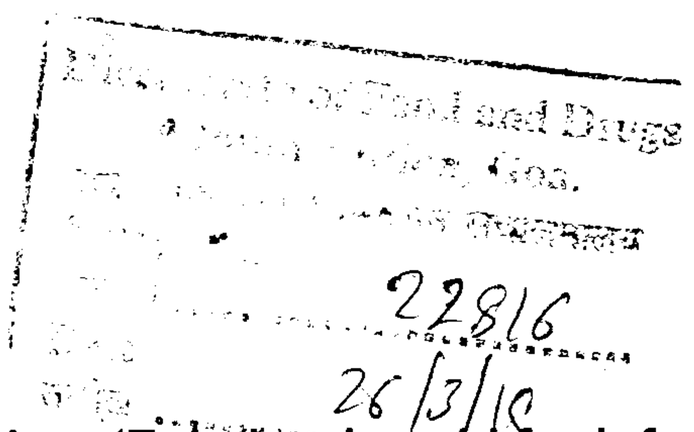
138

Cipla

Date: 26.03.2018



To,
Ms Jyoti Sardesai,
Director, Food and Drug Administration,
Dhanwantari, Opp. Shrine of the Holy Cross,
Bambolim Goa 403202.

Sub: Adverse Drug Reaction of Rokfos Infusion, (Zoledronic acid for infusion 5mg/100ml) Batch No. V40056.

Dear Madam,

We acknowledge the receipt of your letter No. 31/DFDA/68B/2017-18/7682 dated 21.02.2018, we are herewith submitting response from our Drug Safety Department on above letter.

Kindly acknowledge the receipt of this letter.

Thanking you.
Yours faithfully,
For Cipla Limited.

Viraj Sinari
(Authorised Signatory)

Cipla Ltd. M - 61, M - 62, M - 63 & N-5, Verna Industrial Estate, Verna, Salcette, Goa - 403722.
Tel (0832) 2889900
Cipla Ltd. Regd. Office Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai - 400 013
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Corporate Identity Number L24239MH1935PLC002380

Cipla

Date: 26.03.2018

Ms Jyoti Sardesai,
Director, Food and Drug Administration,
Dhanwantari,
Opp. Shrine of the Holy Cross,
Bambolim Goa 403202.

Sub: Explanation to notice received fo · Adverse Drug Reaction of Rokfos Infusion,
Batch No. V40056.

Dear Madam,

Thank you for the time for the personal hearing on 23rd March 2018. It was indeed a pleasure to meet you personally.

Here is our submission as discussed in the personal hearing.

1. We have performed investigation on the batch in question of Rokfos i.e. batch V40056 and following are the findings of the investigation:
   i. We would like to confirm that the complaint batch V40056 which was manufactured and at our Cipla Location Unit IX is already expired in January 2016 having shelf life of 24 months.
   ii. Further detail review performed and found that all the raw materials and packing components used in the said batch were procured from approved suppliers and used in the batch after testing and release from Quality Control department.
   iii. The entire process including manufacturing, filtration, filling, sealing, terminal sterilization and visual inspection was reviewed and was found satisfactory. In-process checks including temperature and pH of manufactured bulk was checked and found satisfactory.
   iv. The environmental parameters including temperature and relative humidity during batch processing was reviewed and found satisfactory. Additionally, the environmental monitoring data including the viable and non-viable count was reviewed and found satisfactory.
   v. The analytical test report of the said batch was reviewed and the results of chemical as well as microbiological test was found to be well within the specification limit.
   vi. The stability data of the product was reviewed and the product is stable up to its shelf life.

2. Cipla has submitted the CIOMS forms to DCGI and PVPI within the stipulated timeframe every time a follow-up was received.

3. We were unaware of the fact that Schedule M mandates that "Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority."

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4. We have performed adequate follow-up for the case but did not get conclusive evidence on whether Cipla product Rokfos was indeed used.

5. Causality with Cipla product was unassesable and we believe the death is not attributable to Cipla Rokfos because –
    a. There was a mismatch between the doctor's words which mentions he thought he gave "Zobone", nursing records say that "IV Zolebon" but the carton of Rokfos was attached to the in-patient records.
    b. It was reported that Rokfos was administered without patient's consent, without bone density tests or MRI and without conducting the most crucial creatinine clearance test.
    c. There was no information on concomitant medications or concurrent conditions except for the history of bone tuberculosis.
    d. Aplastic anemia is not listed in Cipla PI as well as in innovator PI (Novartis Reclast)

6. As discussed in the personal hearing, Cipla will make the following changes to its processes -
    a. Cipla will conduct product quality investigations for all death cases resulting from the use of a Cipla drug if the batch number is known.
    b. It is Cipla's responsibility to find out the manufacturing site of the drug involved. Cipla will try it's best to find out the manufacturing site for reporting purposes.
    c. Cipla shall submit reports of serious adverse drug reactions resulting from the use of the drug along with comments and documents to the concerned licensing authority. If Cipla cannot zero-in on the manufacturing site, Cipla will report serious cases to all applicable licensing authorities in addition to DCGI and PVPI.

7. We are additionally submitting
    a. Latest CIOMS form
    b. Rokfos case details – slide deck
    c. Response from our Medical Services team.

Kindly acknowledge the receipt of this letter.

Thanking you.
Yours Sincerely,

26.03.2018

Dr. Avinash R. Kakade
Head Global Pharmacovigilance
Cipla Ltd.

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CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1 PATIENT INITIALS (first, last)	1a COUNTRY	2 DATE OF BIRTH Day	Month	Year	2a AGE	3 SEX	3a WEIGHT	4-5 REACTION ONSET Day	Month	Year
PRIVACY	INDIA		Unk		45 Years	Female	Unk	10	JUN	2014

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas)

Other Serious Criteria: Important medical event
Aplastic anaemia [Aplastic anaemia]
Arthralgia/bone pain/back pain [Arthralgia]
Dysphagia [Dysphagia]
Myalgia [Myalgia]

Case Description: Initial receipt date: 06-Aug-2014

Follow-up 1 receipt date: 16-Aug-2014

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [x] PATIENT DIED Date: 24-JUN-2014
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- [ ] INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING
- [ ] CONGENITAL ANOMALY
- [x] OTHER: Important medical event

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) (include generic name)
#1) ZOLEDRONIC ACID (ZOLEDRONIC ACID) Injection {Lot # V40056; Exp.Dt. JAN-2016}

15 DAILY DOSE(S)
#1) 5mg/100 ml, I V. infusion

16 ROUTE(S) OF ADMINISTRATION
#1) Intravenous

17 INDICATION(S) FOR USE
#1) Mild osteoporosis (Osteoporosis)

18 THERAPY DATES(from/to)
#1) 10-JUN-2014 / Unknown

19 THERAPY DURATION
#1) Unknown

20 DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21 DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22 CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23 OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Concurrent condition	Tuberculosis of spine (Bone tuberculosis)
Unknown to Ongoing	Concurrent condition	Arm paralysis (Monoplegia)

IV. MANUFACTURER INFORMATION

24a NAME AND ADDRESS OF MANUFACTURER
Cipla Ltd.
Avinash Kakade

26 REMARKS
Medically Confirmed: Yes
World Wide #: IN-CIPLA LTD -2014IN01075

24b MFR CONTROL NO
2014IN01075

24c DATE RECEIVED BY MANUFACTURER
05-MAR-2018

24d REPORT SOURCE
☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☒ OTHER Spontaneous

DATE OF THIS REPORT
06-MAR-2018

25a REPORT TYPE
☐ INITIAL ☒ FOLLOWUP 4

25b NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD

NAME AND ADDRESS WITHHELD

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up 2 receipt date: 26-Aug-2014

Follow-up 3 receipt date: 07-Jul-2016

Follow-up 4 receipt date: 18-Apr-2017

Follow-up 5 receipt date: 23-Jan-2018

Follow-up 6 receipt date: 27-Feb-2018

Information was received from a consumer via physician concerning a 45-year-old female patient, who received Rokfos (zoledronic acid).

The patient's medical history and concomitant medications were not reported. The patient's concurrent conditions included spinal tuberculosis, cervical spondylitis, arthralgia and one paralytic arm.

On an unknown date, the patient received one shot of steroid for tuberculosis treatment. On 09-Jun-2014, the patient came with complaint of stiff Neck and cervical spondylitis. X-ray of cervical spine confirmed osteoporosis (mild). The reporter stated that, on 10-Jun-2014, after all necessary investigations of complete blood count and appropriate hydration, the patient was administered Rokfos 5mg/100 ml as an intravenous infusion (batch no: V40056, manufactured date: Feb-2014, expiry date: Jan-2016). It was reported that Rokfos was administered without patient's consent, without bone density tests or MRI Scan and without conducting the most crucial Creatinine Clearance Test. On 10-Jun-2014, MRI was done it showed cord compression and surgery was fixed on 16-Jun-2014.

On 10-Jun-2014 (within 24 hours of Rokfos administration), the patient experienced severe arthralgia, myalgia, bone pain and back pain. On 11-Jun-2014, the patient experienced dysphagia and petechial rashes appeared on arms and legs. On 12-Jun-2014, patient experienced pancytopenia, WBC fell from 20,080 to 2,300 in a single day and platelets fell from 143,000 to 95,000. On 13-Jun-2014, platelets fell again from 95,000 to 59,000 (units unspecified). All the possible adverse reactions noticed by the physician, but, the physician ignored blatantly and replied that "This was the effect of Rokfos working on all 206 bones of the body simultaneously and that these reactions will go in 3 to 4 days time". Blood counts fell from 143000 platelets to 20000 platelets and WBC from 20000 to 200 within 3 days time. The patient developed worsening of platelet counts with anemia and ultimately diagnosed with aplastic anaemia. The physician mentioned in the in-patient record as arthralgia and rendered her bed ridden. It was reported that on 14-Jun-2014, patient was shifted abruptly, in a panic, on a stretcher without any details of treatment, diagnosis, tests conducted and condition of the patient, except "Shift to Platinum for Surgery". Platinum Hospitals admitted the patient and conducted necessary tests for surgical fitness. Within one hour she was declared critical and shifted to ICU. Thereafter she was shifted to Jupiter Hospital. On 24-Jun-2014, after 16 days of administering Rokfos, the patient expired due to aplastic anaemia at Jupiter Hospital. Treatment and lab details were not provided. On 22-Oct-2014, the consumer reported this adverse drug reaction to Central Drugs Standard Control Organisation.

Action taken with Rokfos was not applicable. The outcome of the event of aplastic anaemia was fatal. Outcome of arthralgia, dysphagia and myalgia was unknown.

Initially, the physician commented that this was the first time that this drug has caused such severe reactions and also mentioned that aplastic anaemia could be due to spinal tuberculosis and not due to Zoledronic acid. But, the consumer wants to investigate the causes leading to the patient's death which was due to "Aplastic Bone Marrow" reason being drug induced. Finally, the physician was not clear regarding the drug administered. The physician says he thought he gave Zobone but actually gave Rokfos. Nursing records says "IV Zolebon" and there was no IV Rokfos mentioned. Only the outer box of the drug was attached to In-Patient records.

The company physician considered the event aplastic anaemia as serious according to the seriousness criterion of Death and arthralgia as serious with the seriousness criterion of other-important medical events and the events dysphagia, myalgia were considered as non-serious.

Follow up information received by consumer on 16-Aug-2014: Patient husband reported that his wife was diagnosed for cervical spondylitis with pain in the neck when Zoledronic acid was given to the patient on admission to the nursing home. No additional information received.

Follow up information received by consumer on 26-Aug-2014: Patient's husband reported that mild osteoporosis was seen in the patient for which Rokfos was given. The adverse reactions started within 24 hours of taking Rokfos. Blood counts fell from 143000 platelets to 20000 platelets in the nursing home and WBC from 20000 to 200 within 3 days. Additionally, reporter mentioned that Arthralgia caused her bed ridden till her death on 24-June-2014.

Follow up information received by consumer on 07-Jul-2016 (significant follow-up): The patient's husband reported the adverse drug reaction to the CDSCO. The physician's comment on the drug administered was updated. Narrative was updated accordingly.

143

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up information received on 18-Apr-2017 (significant information): Information about lab data (x-ray, result of MRI, platelet and WBC count), three new events (arthralgia, dysphagia, myalgia) added. Narrative amended accordingly.

Follow up received on 23-Jan-2018 (Non-significant follow up): No new information was received.

Follow-up received on 27-Feb-2018 (Non-significant follow up): No new information was received.

Significant correction on 05-Mar-2018: Company comment and seriousness criteria of event dysphagia updated (upgraded from non-serious to serious).

Company Comment: It was reported, though inconclusively, that the patient was administered IV ROKFOS. Within 3 days, the blood counts started dropping. Aplastic Anaemia was diagnosed and patient died after 16 days of administering ROKFOS. Aplastic Anaemia is not a listed event in pack insert of Cipla as well as in the USPI of Reclast (Novartis). The physician was unclear about which was the drug administered. It was reported that the physician says he thought he gave zobone but actually gave Rokfos. Nursing records says IV Zolebon and there was no IV Rokfos mentioned. Only the outer box of the drug was attached to in-patient records. Thus, it was not conclusively informed that the patient really received IV Rokfos. It was reported that Rokfos was administered without patient's consent, without bone density tests or MRI Scan and without conducting the most crucial Creatinine Clearance Test. The concomitant medications were not reported. In view of this inconclusive and incomplete information, the causal relationship of IV Rokfos to the events is unassessable.

13. Relevant Tests

MRI (unknown date, one day after receiving Rokfos): Cord compression.

X-ray (unknown date): Mild osteoporosis.

Platelet count (unknown date): Fell from 143000 to 20000 in 3 days (depressed).

WBC count (unknown date): Fell from 20000 to 200 in 3 days (depressed).

Platelet count (12-Jun-2014): Fell from 143,000 to 95,000 (units unspecified).

WBC count (12-Jun-2014): Fell from 20,080 to 2,300 (units unspecified) in a single day.

Platelet count (13-Jun-2014): Fell again from 95,000 to 59,000 (units unspecified).

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Concurrent condition	Cervical spondylosis (Spinal osteoarthritis);
Unknown to Ongoing	Concurrent condition	Arthralgia (Arthralgia);

The patient was 45 years old and presented with complaint of stiff neck. She was diagnosed with mild osteoporosis using x-ray of cervical vertebrae. Osteoporosis is an old age disease and usually occur after the age of 50 years. Also, X-ray is commonly used to diagnose osteoporotic fractures only. Bone Mineral Density test is the most common osteoporosis diagnostic tool which was not done in this case. Stiff neck could be due to cervical spondylitis (patient's concomitant condition).

Zoledronic acid should not be given in case of renal impairment. However, whether creatinine clearance test was done or not is contradictory. As per the doctor, it was done; while according to reporter it wasn't done.

According to reporter, ROKFOS was administered to the patient without her consent.

Nursing records suggest that ZOBONE (5mg) was prescribed to the patient. The outer carton attached in in-patient records was of ROKFOS. However, doctor was not clear whether he had given ZOBONE or ROKFOS to the patient.

It is unclear whether patient was osteoporotic or not and ROKFOS was administered to the patient or not.

Incidences of aplastic anaemia reported to FDA:

- After Zoledronic acid administration- As per the FDA reports, incidence of aplastic anaemia after zoledronic acid administration was 0.01% of total reported side effects (1 out of 8,807 people). This one patient was taking paclitaxel (Taxol), tamoxifen and cyclophosphamide concomitantly. As per FDA report, the incidence of aplastic anaemia due to these drugs are 0.02%, 0.31% and 0.12%, respectively.
  https://www.ehealthme.com/ds/zoledronic-acid/aplastic-anaemia/
  https://www.ehealthme.com/ds/paclitaxel/aplastic-anaemia/
  https://www.ehealthme.com/ds/tamoxifen-citrate/aplastic-anaemia/
  https://www.ehealthme.com/ds/cyclophosphamide/aplastic-anaemia/
  This data indicates that aplastic anaemia could be due to other drugs as well (in our case, apart from zoledronic acid) and thus patient's information regarding concomitant medications is required.
- After ZOMETA (zoledronic acid- 4mg) administration- ZOMETA is approved for the treatment of hypercalcemia due to malignancy. Aplastic anaemia incidence after ZOMETA administration was found to be 0.16% and none of them were developed within one month of administration.
  https://www.ehealthme.com/ds/zometa/aplastic-anaemia/
- Prednisolone (steroid): Aplastic anaemia incidence after prednisolone administration was found to be 0.17% and 58.62% of them were developed within one month of administration.
  The unknown steroid which was administered on unknown date could also be the cause of aplastic anaemia.
  https://www.ehealthme.com/ds/prednisolone/aplastic-anaemia/

Zoledronic acid (5mg) prescribing information:

Aplastic anaemia is not reported in prescribing information of zoledronic acid. As per the clinical trial studies, no marrow fibrosis was found in bone histology after zoledronic acid administration.

Concomitant conditions and drugs:

The patient was suffering from spinal tuberculosis (TB) and cervical spondylitis. However, the concomitant drugs are not mentioned. As per a study, the major haematological disorder due to anti-TB drug is aplastic anaemia. Williams et al. reported three cases of aplastic anaemia occurring in association with anti-tubercular therapy. All the three patients died of haemorrhage secondary to thrombocytopenia, consistent with an irreversible damage of the bone marrow. There are reports of petechiae due to antitubercular drugs.

Patient symptoms:

The patient was suffering from arthralgia which is a reported common side effect of zoledronic acid. However, it resolves within 2-3 days or may last up to 7-14 days. Whereas, in this case the patient was bed-ridden.

Petechial rash was also seen on patient's body. It could be either due to bone marrow failure or medication (including zoledronic acid and anti-tubercular drugs) induced.

As per the data mentioned above, no strong correlation seems to exist between the occurrence of aplastic anaemia and ROKFOS administration. Concomitant medications (e.g. steroid, anti-tubercular drugs) and existing spinal tuberculosis as the cause of its occurrence cannot be ruled. Also, to begin with, it remains unclear whether zoledronic acid administration was required at all.

146

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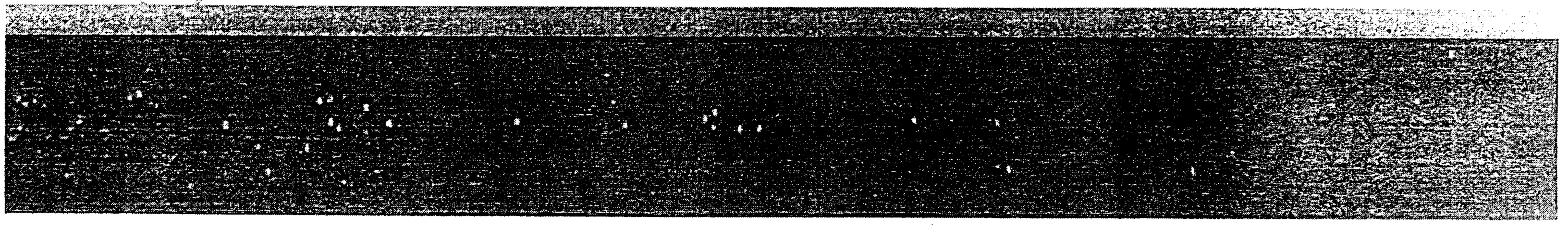
Rokfos Infusion Case Details

Zoledronic acid for infusion 5mg/100ml
Batch number: V40056
Drug Safety Case number : 2014IN01075



146

Detailed Information

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Sr no	Date sequence	Information
01	IRD: 06-Aug-2014	First time information was received from Medical Services team (Mr Shekhar Gitaye) to Drug safety via Umeshchandra Barkur (Reporter: Husband of deceased)
02	07-Aug-2014	Mr Shekhar Gitaye called the Dr Mihirgiri Goswami
03	16-Aug-2014	Reporter emailed to PRC/RA/VKH R&D (Dr Purandare)
04	16-Aug-2014	Dr Purandare forwarded received information to Dr Gogtay for advice
05	20-Aug-2014	Initial Case was submitted to DCGI
06	26-Aug-2014	Follow up received from reporter and was asking for official response and other case related information provided
07	27-Aug-2017	Dr Abhay has replied to reporter via drug safety email
08	08-Sep-2014	First follow up was submitted to DCGI
09	07-Jul-2016	Second follow up was received from reporter. Response from reporter and other other case related information provided

147

Detailed Information

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Sr no	Date sequence	Information
10	21-Jul-2016	Second follow up was submitted to DCGI
11	18-Apr-2017	Third follow up received from reporter. He has sent letter to Managing Director of Cipla
12	02-May-2017	Third follow up was submitted to DCGI
13	18-Jan-2018	Letter received from Goa State FDA to Cipla Goa Unit
14	23-Jan-2018	Response provided to Goa State FDA (Letter signed by Mr Ashwin Upasane)
15	12-Feb-2018	Response received from Goa State FDA
16	14-Feb-2018	Response provided to Goa State FDA (Letter signed by Dr Avinash)
17	04-Mar-2018	Letter received from Goa State FDA to Cipla Goa Unit for personal hearing
17	06-Mar-2018	Follow up processed and submitted to DCGI
18	07-Mar-2018	Acknowledgement received from DCGI

148

PSUR submission details

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Cipla has submitted a total of six PSUR covering four-year period starting from date of approval complying the requirement for permission to manufacture of new drugs for sale. The schedule of PSURs with their review period and date of submission is as presented in table below.

Sr.	Frequency of submission	Review period	Submission acknowledgment receipt date
1	Six monthly	20.07.2010 to 31.01.2011	06.06.2011
2	Six monthly	01.02.2011 to 31.07.2011	26.08.2011
3	Six monthly	01.08.2011 to 31.01.2012	21.03.2012
4	Six monthly	01.02.2012 to 31.07.2012	28.08.2012
5	Annual	01.08.2012 to 31.07.2013	20.08.2013
6	Annual	01.08.2013 to 31.07.2014	27.08.2014

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Thank you