F.No.12-01/18-DC(Pt-238)
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
New Drugs Division

FDA Bhawan, Kotla Road
New Delhi
Dated: 19.12.2018

To
All State/UT Drugs Controllers

Subject: - Safety guidelines for Isotretinoin - Regarding

Sir/Madam,

Isotretinoin is an oral drug used for the treatment and prevention of severe acne.

Isotretinoin capsule 10mg/ 20mg was approved by CDSCO on 21.06.2002 for treatment of cystic and conglobate acne, severe nodular acne unresponsive to antibiotic therapy with various conditions including a box warning for female patients as the drug may cause severe birth defects and patients should sign a consent form as per specified format before undertaking the treatment of Isotretinoin. Copy of the approval/permission is enclosed for ready reference.

In light of concerns raised with regard to safety of Isotretinoin, the matter has been examined by CDSCO in consultation with the Subject Expert Committee (SEC) (Dermatology & Allergy) in its meeting held on 26.07.2018.

The SEC deliberated the matter in detail and opined that the drug has favorable risk/benefit profile for the indications approved in the country. However, the following conditions should be followed during manufacture, sale and distribution of the drug as already stipulated by CDSCO at the time of approval of the drug.

1. The drug should be sold by retail on the prescription of Dermatologists only.
2. Pack of the drug should carry following Box warning-

   > This medicine may cause severe birth defects; you must not take this medicine if you are pregnant or may likely become pregnant during treatment.
   >
   > You should also avoid pregnancy for 6 months after stopping the treatment.

3. The patients should also sign a Consent Form before undertaking the treatment of Isotretinoin as already stipulated in the new drug permission.

The committee also recommended that the manufacturers should provide package insert along with their product which should be in major vernacular languages. The retail chemists should maintain the details of retail sale of the drug which should be strictly on the prescription of Dermatologist only.

Accordingly, you are requested to direct the manufacturers/retail chemists under your jurisdiction to comply with the following:-

(i) For Manufacturers:

1. Label should contain the warning 'The drug should be sold by retail on the prescription of Dermatologists only.'

2. Pack of the drug should carry following Box warning-

This medicine may cause severe birth defects; You must not take this medicine if you are pregnant or may likely become pregnant during treatment. You should also avoid pregnancy for 6 months after stopping the treatment.

3. The patients should also sign a consent form before undertaking the treatment of Isotretinoin as per the format enclosed.

4. Manufacturer should provide package insert along with their product which should be in major vernacular languages.

(ii) For retailers:

The drug should be sold by retail only on prescription of Dermatologist and the details of the sale should be strictly maintained as per requirements of D&C Rules, 1945.

Action taken in this regard may be intimated to this office.

Yours faithfully

(Dr. S. Eswara Reddy)
Drugs Controller General (India)

Copy for information and necessary follow up to:

All Zonal/Sub Zonal offices of CDSCO.

CDSCO website.

Patient Information/Informed Consent (for all patients):

A. To be completed by patient (and parent or guardian if patient is under age 18) and signed by the doctor.

Read each item below and initial in the space provided if you understand each item and agree to follow your doctor's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.

Do not sign this agreement and do not take isotretinoin if there is anything that you do not understand about all the information you have received about using isotretinoin.

1. I, _____,
   (Patient's Name)

   Understand that isotretinoin is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.

   Initials: _____

2. I understand that I must not get pregnant 1 month before, during the entire time of my treatment, and for 6 month after the end of my treatment with isotretinoin.

   My doctor has told me about my choices for treating my acne.

   Initials: _____

3. I understand that there are serious side effects that may happen while I am taking isotretinoin. These have been explained to me. These side effects include serious birth defects in babies of pregnant patients. (Note: There is a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)

   Initials: _____

4. I understand that some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental problems. Symptoms of depression include sad, "anxious" or empty mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking isotretinoin have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on isotretinoin becoming aggressive or violent. No one knows if isotretinoin caused these behaviors or if they would have happened even if the person did not take isotretinoin. Some people have had other signs of depression while taking isotretinoin (see #7 below).

Initials: _____

5. Before I start taking isotretinoin, I agree to tell my doctor if I have ever had symptoms of depression (see #7 below), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

   Initials: _____

6. Before I start taking isotretinoin, I agree to tell my doctor if, to the best of my knowledge, anyone in my family has ever had symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.

   Initials: _____

7. Once I start taking isotretinoin, I agree to stop using isotretinoin and tell my doctor right away if any of the following signs and symptoms of depression or psychosis happen. I:

   - Start to feel sad or have crying spells
   - Lose interest in activities I once enjoyed
   - Sleep too much or have trouble sleeping
   - Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
   - Have a change in my appetite or body weight
   - Have trouble concentrating
   - Withdraw from my friends or family
   - Feel like I have no energy
   - Have feelings of worthlessness or guilt
   - Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
   - Start acting on dangerous impulses
   - Start seeing or hearing things that are not real

   Initials: _____

8. **I agree to return to see my doctor every month I take isotretinoin to get a new prescription for isotretinoin, to check my progress, and to check for signs of side effects.**

   Initials: _____

9. Isotretinoin will be prescribed just for me — I will not share isotretinoin with other people because it may cause serious side effects, including birth defects.

   Initials: _____

10. I will not give blood while taking isotretinoin or for 1 month after I stop taking isotretinoin. I understand that if someone who is pregnant gets my donated blood, her baby may be exposed to isotretinoin and may be born with serious birth defects.

Initials: _____

11. I have read the materials my provider gave me containing important safety information about isotretinoin. I understand all the information I received.

    Initials: _____

B. <u>For female patients who can get pregnant</u>

1. I understand that there is a very high chance that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking isotretinoin. This can happen with any amount and even if taken for short periods of time. This is why I must not be pregnant while taking isotretinoin.

   Initial: _____

2. I understand that I must not get pregnant 1 month before, during the entire time of my treatment, and for 6 months after the end of my treatment with isotretinoin.

   Initial: _____

3. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) at the same time. The only exceptions are if I have had surgery to remove the uterus (a hysterectomy) or both of my ovaries (bilateral oophorectomy), or my doctor has medically confirmed that I am post-menopausal.

   Initial: _____

4. I understand that hormonal birth control products are among the most effective forms of birth control. Combination birth control pills and other hormonal products include under-the-skin implants, vaginal rings, and intrauterine devices (IUDs). Any form of birth control can fail. That is why I must use 2 different birth control methods at the same time, starting 1 month before, during, and for 6 months after stopping therapy every time I have sexual intercourse, even if 1 of the methods I choose is hormonal birth control.

   Initial: _____

5. I understand that the following are effective forms of birth control:

Primary forms	Secondary forms
• tying my tubes (tubal sterilization) • partner's vasectomy • intrauterine device • hormonal (combination birth control pills, under the-skin implants, or vaginal ring)	*Barrier:* • male latex condom with or without spermicide • vaginal sponge (contains spermicide)

I understand that at least 1 of my 2 forms of birth control must be a primary method.

Initial: _____

6. I will talk with my doctor about any medicines including herbal products I plan to take during my isotretinoin treatment because hormonal birth control methods may not work if I am taking certain medicines or herbal products.

   Initial: _____

7. I must begin using the birth control methods I have chosen as described above at least 1 month before I start taking isotretinoin.

   Initial: _____

8. I cannot get my first prescription for isotretinoin unless my doctor has told me that I have 2 negative pregnancy test results. The first pregnancy test should be done when my doctor decides to prescribe isotretinoin. The second pregnancy test must be done in a lab during the first 5 days of my menstrual period right before starting isotretinoin therapy treatment, or as instructed by my doctor. I will then have 1 pregnancy test; in a lab.
   - every month during treatment
   - at the end of treatment
   - and 1 month after stopping treatment

   I must not start taking isotretinoin until I am sure that I am not pregnant, have negative results from 2 pregnancy tests, and the second test has been done in a lab.

   Initial: _____

9. I have read and understand the materials my doctor has given to me.

   I was told about a private counselling line that I may call for more information about birth control. I have received information on emergency birth control.

   Initial: _____

10. I must stop taking isotretinoin right away and call my doctor if I get pregnant, miss my expected menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods at any time.

    Initial: _____

11. My doctor has answered all my questions about isotretinoin and I understand that it is my responsibility not to get pregnant 1 month before, during isotretinoin treatment, or for 6 months after I stop taking isotretinoin.

    Initial: _____

12. My doctor and I have decided I should take isotretinoin. I understand that I must be qualified to have my prescription filled each month. I understand that I can stop taking isotretinoin at any time. I agree to tell my doctor if I stop taking isotretinoin.

    Initials: _____

I now allow/authorize my doctor _____ to begin my treatment with isotretinoin.

Patient Signature: _____ Date: _____

Parent/Guardian Signature (if under age 18): _____ Date: _____

Patient Name (print) _____

Patient Address

_____

_____

Telephone (_____)

I have:

• Fully explained to the patient, _____, the nature and purpose of isotretinoin treatment, including its benefits and risks, risks to female patients of child bearing potential.

•Given the patient the appropriate educational materials, and asked the patient if he/she has any questions regarding his/her treatment with isotretinoin

• Answered those questions to the best of my ability

Doctor Signature: _____ Date: _____

F.No. 12-30/95-DC

From:

The Drugs Controller General (India)
Dte. General of Health Services

New Delhi, dated 13 JUN 2002

Dear Sirs,

Please refer to your letter dated 16th January, 2001 & subsequent correspondence regarding the manufacture of Isotretinoin Capsules USP

Permission is hereby granted to the manufacture of the formulation mentioned above under Rule 122-B of the Drugs & Cosmetics Rules subject to the following conditions:-

1. The product shall have the following composition:-
   Each soft gelatine Capsules contains:-
   Isotretinoin USP————10 mg / 20mg

2. Post Marketing surveillance study shall be conducted during initial period of two years of marketing of the new drug formulation after getting the protocol and the names of the investigator duly approved by the Licensing Authority

3. This Directorate should be intimated as and when the said formulation is launched by you in the Indian Market and submit sale pack containing one unit of the medicine.

4. The proper name of the drug Isotretinoin Capsules of and shall be printed or written in indelible ink and shall appear in a more conspicious manner than the trade name if any, which shall be shown immediately after or under the proper name on the label of the innermost container of the drug or every other covering in which the container is packed.

5. The label of the innermost container of the drug and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which shall not be less that 1mm in width and without disturbing the other conditions printed on the label to depict it is a prescription drug.

Contd on page——2

1/4

6. The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:-

WARNING: " To be sold by retail on the prescription of a Dermatologist only

7. The drug will be required to be withdrawn from sale from the market in-case any undesirable reactions due to its medication is brought to light at any stage. This Directorate should be informed of adverse reaction on the drug, if any.

8. The preparation shall be indicated in treatment of cystic and conglobate acne, severe nodular acne unresponsive antibiotic therapy

9. No claims except those mentioned above shall be made for this drug without the prior approval of this Directorate

10. No reference in the advertisement or medical literature is made that the Government has approved the drug.

11. Drafts of the carton labels, package insert or any other promotional literature etc. that will be adopted by you for marketing this drug in the country should be got approved from this Directorate before the drugs is marketed.

12. This permission is no way relieves you of the responsibility of complying with all other provisions of the Drugs and Cosmetics Act and the Rules thereunder.

13. Package Insert should carry a box warning at a prominent place about potential risk Involved in usage of Isotretinoin and a diagram warning pregnant women against taking Isotretinoin.

14. Pack should carry following box warning:-

WARNING TO FEMALE PATIENTS:-
THIS MEDICINE MAY CAUSE SEVERE BIRTH DEFECTS. YOU MUST
NOT TAKE THIS MEDICINE IF YOU ARE PREGNANT OR MAY
LIKELY BECOME PREGNANT DURING TREATMENT.

15. The patients should sign a consent form as per the enclosure before undertaking the treatment of Isotretinoin.

Kindly note that permission granted above is liable to be withdrawn if any of the conditions stipulated above are not complied with apart from any other action that may be taken under provisions of the Drugs & Cosmetics Act 1940 and the Rules thereunder.

Yours faithfully,

(Ashwini Kumar)
Drugs Controller General (India)