Amendments to relevant sections of the Product Information as approved by the CHMP on 22 March 2018, pending endorsement by the European Commission

Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Teratogenic effects

For all oral retinoids containing acitretin, alitretinoin and isotretinoin, *the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below*

Summary of product characteristics

As these products will now be subject to additional monitoring the black symbol and relevant statement should be included preceding section 1.

The warning regarding teratogenic effects and information on the pregnancy prevention programme should be aligned with the following text; furthermore a boxed warning as presented below should be added:

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

[…]

4.4 Special warnings and precautions for use

Teratogenic effects
[TRADENAME] is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.
[TRADENAME] is strictly contraindicated in:
- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC

[INN] is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- [*approved indications*] (see section 4.1 „Therapeutic indications“).
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month [3 years for acitretin] after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.

    o [for acitretin this last bullet point should be]

- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of [INN].

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month [3 years for acitretin] after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

    [for acitretin this last bullet point should be]

- Negative pregnancy test results have been obtained before, during and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with [INN], treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within one month following the end of treatment [3 years for acitretin].

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting

treatment, throughout treatment and continue for at least 1 month [3 years for acitretin] after stopping treatment with [INN], even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mUI/mL are recommended to be performed, as follows.

Prior to starting therapy

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with [INN].

Follow-up visits

Follow-up visits should be arranged at regular intervals, ideally monthly. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

1 month after stopping treatment, women should undergo a final pregnancy test.

[for acitretin this last paragraph should be]

Women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of [TRADENAME] should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of [TRADENAME] should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients

The available data suggest that the level of maternal exposure from the semen of the patients receiving [TRADENAME], is not of a sufficient magnitude to be associated with the teratogenic effects of [TRADENAME]. Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month [3 years for acitretin] following discontinuation of [INN] because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding fetal exposure to [INN] the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of [INN], to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Labelling

A boxed warning should be added to the outer packaging for the oral retinoids **acitretin, alitretinoin and isotretinoin** as follows:

Particulars to appear on the outer packaging
Outer carton

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or think you may be pregnant

Package Leaflet

The warning regarding teratogenic effects and information on the pregnancy prevention programme should be aligned with the following text; furthermore a boxed warning as presented below should be added:

Boxed warning

The following boxed warning should be included in the PL for the oral retinoids **acitretin, alitretinoin and isotretinoin**, under the invented name:

{(Invented) name strength pharmaceutical form}

{Active substance(s)}

WARNING

CAN SERIOUSLY HARM AN UNBORN BABY

Women must use effective contraception

Do not use if you are pregnant or you think you may be pregnant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects

Section 2. What you need to know before you take <TRADENAME>

Do not take <TRADENAME>

- If you are pregnant or breast-feeding.
- If there is any chance you could become pregnant, you must follow the precautions under "Pregnancy and prevention programme", see section on "Warnings and precautions".

Women who are pregnant must not take <TRADENAME>

This medicine can seriously harm an unborn baby (the medicine is said to be 'teratogenic') – it can cause serious abnormalities of the unborn baby's brain, face, ear, eye, heart and certain glands (thymus gland and parathyroid gland). It also makes a miscarriage more likely. This may happen even if <TRADENAME> is taken only for a short time during pregnancy.

- You must not take <TRADENAME> if you are pregnant or if you think you might be pregnant.
- You must not take <TRADENAME> if you are breastfeeding. The medicine is likely to pass into your milk and may harm your baby.
- You must not take <TRADENAME> if you could get pregnant during treatment.
- You must not get pregnant for one month after stopping this treatment because some medicine may still be left in your body.
- for acitretin this last bullet point should be:
- You must not get pregnant for 3 years after stopping this treatment because some medicine may still be left in your body.

Women who could get pregnant are prescribed <TRADENAME> under strict rules. This is because of the risk of serious harm to the unborn baby

These are the rules:

- Your doctor must explain the risk of harm to the unborn baby - you must understand why you must not get pregnant and what you need to do to prevent getting pregnant.

- You must have talked about contraception (birth control) with your doctor. The doctor will give you information on how not to get pregnant. The doctor may send you to a specialist for contraception advice.
- Before you start treatment, your doctor will ask you to take a pregnancy test. The test must show that you are not pregnant when starting treatment with <TRADENAME>

Women must use effective contraception before, during and after taking <TRADENAME>

- You must agree to use at least one very reliable method of contraception (for example an intra uterine device or contraceptive implant) or, two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your doctor which methods would be suitable for you.
- You must use contraception for a month before taking <TRADENAME>, during treatment and for a month afterwards [for acitretin should be during 3 years]
- You must use contraception even if you do not have periods or you are not sexually active (unless your doctor decides this is not necessary).

Women must agree to pregnancy testing before, during and after taking <TRADENAME>

- You must agree to regular follow-up visits, ideally every month.
- You must agree to have regular pregnancy tests, ideally every month during treatment and, because some medicine may still be left in your body, 1 month after stopping <TRADENAME> (unless your doctor decides this is not necessary in your case). [for acitretin: 'every 1 to 3 months for 3 years after stopping <TRADENAME>']
- You must agree to extra pregnancy tests if your doctor asks you.
- You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body.
- for acitretin this last bullet point should be:
- You must not get pregnant during treatment or for 3 years afterwards because some medicine may still be left in your body.
- Your doctor will discuss all these points with you, using a checklist and will ask you (or a parent/guardian) to sign it. This form confirms that you have been told about the risks and that you will follow the rules above.

If you get pregnant while taking <TRADENAME>, **stop taking the medicine straight away,** and contact your doctor. Your doctor may send you to a specialist for advice.

Also, if you become pregnant within one month *[3 years for acitretin]* after you stop taking <TRADENAME>, you should contact your doctor. Your doctor may send you to a specialist for advice.

Advice for men

The levels of oral retinoid in the semen of men taking <TRADENAME> are too low to harm their partners' unborn baby. However, you must never share your medication with anyone.

Additional precautions

You should never give this medicinal product to another person. Please take any unused <capsules> to your pharmacist at the end of treatment.

You should not donate blood during treatment with this medicine and for 1 month [3 years for acitretin] after stopping <TRADENAME> because an unborn baby could be harmed if a pregnant patient receives your blood.

Pregnancy, breast-feeding and fertility

For more information on pregnancy and contraception, see section 2 ”Pregnancy and prevention programme”.

The following sentence should be included at the end of the package leaflet (last sentence):

<Detailed and updated information on this product is available by scanning the QR code included in the PL with a smartphone. The same information is also available on the following URL: *[URL to be included] <and the <NCA> website >>.*

‘*QR code to be included*’ + <URL>

Neuropsychiatric disorders

For all oral retinoids containing acitretin, tretinoin and bexarotene, *the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below.*

Summary of product characteristics

The warning on psychiatric disorders should be revised as follows:

Section 4.4 Special warnings and precautions for use

Psychiatric disorders

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including <INN>. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

Package leaflet

The warning on psychiatric disorders should be revised as follows:

Section 2 Warnings and precautions

Talk to your doctor before taking <TRADENAME>**:**

- If you have ever had any mental health problems including depression, aggressive tendencies or mood changes. This is because taking <TRADENAME> may affect your mood.

Mental health problems

You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that this medicine could affect your mood and behaviour. They may notice these changes and help you identify any problems that you need to talk to your doctor about.

For all <u>oral</u> retinoids products containing <u>alitretinoin</u> and <u>isotretinoin</u>, *the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below.*

Summary of product characteristics

The warning on psychiatric disorders should be revised as follows:

Section 4.4 Special warnings and precautions for use

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with <INN> (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of <INN> may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Awareness by family or friends may be useful to detect mental health deterioration.

Section 4.8 Undesirable effects

The following adverse reaction(s) should be included under the SOC Psychiatric disorders:

Rare (may affect up to 1 in 1,000 people):

Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.

Very rare (may affect up to 1 in 10,000 people):

Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour

Package leaflet

The warning on psychiatric disorders should be revised as follows:

Section 2. Warnings and precautions

Talk to your doctor before taking <TRADENAME>**:**

- If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes. It also includes thoughts about hurting yourself or ending your life. This is because your mood may be affected while taking <TRADENAME>.

Mental health problems

You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about.

Section 4 Possible side effects

The following adverse reaction(s) should be included:

Mental problems

Rare effects (may affect up to 1 in every 1000 people)

- Depression or related disorders. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort
- Existing depression getting worse
- Becoming violent or aggressive

Very rare effects (may affect up to 1 in every 10,000 people)

- Some people have had thoughts or feelings about hurting themselves or ending their own lives (suicidal thoughts), have tried to end their own lives (attempted suicide), or have ended their lives (suicide). These people may not appear to be depressed.
- Unusual behaviour.
- Signs of psychosis: a loss of contact with reality, such as hearing voices or seeing things that are not there.

Contact your doctor straight away if you get signs of any of these mental problems. Your doctor may tell you to stop taking <TRADENAME>. That may not be enough to stop the effects: you may need more help, and your doctor can arrange this.

For all topical retinoids containing adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene, *the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below.*

Summary of product characteristics

A contraindication should be added as follows:

Section 4.3 Contraindications:

- Pregnancy (see section 4.6)
- Women planning a pregnancy

Section 4.6 Fertility, pregnancy and breastfeeding:

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Pregnancy

<TRADENAME> is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.

If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Package leaflet

A contraindication should be added as follows:

Section 2

Do not use <TRADENAME>:

– If you are pregnant
– If you are planning a pregnancy

[…]

Pregnancy, breastfeeding and fertility:

DO NOT use <TRADENAME> if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information.