VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acne is estimated to affect 9.4% of the global population, making it the eighth most prevalent disease worldwide. Epidemiological studies have demonstrated that acne is most common in postpubescent teens, with boys most frequently affected, particularly with more severe forms of the disease. *(1)*

Moderate-to-severe acne affects around 20% of young people and severity correlates with pubertal maturity. Acne may be presenting at a younger age because of earlier puberty. Acne persists into the 20s and 30s in around 64% and 43% of individuals, respectively. The heritability of acne is almost 80% in first-degree relatives. Acne occurs earlier and is more severe in those with a positive family history. *(2)*

The treatment options include topical therapies and systemic treatments. Topical therapies may be used as monotherapy, in combination with other topical agents or in combination with oral agents in both initial control and maintenance. *(4)*

VI.2.2 Summary of treatment benefits

Because of the risk of adverse effects, which may be severe, the drug should be reserved for patients who are unresponsive to conventional acne therapies, including oral and/or topical anti-infectives. In one study, 20 patients with extensive acne conglobata affecting the face, chest and back, were treated for a period of six months with isotretinoin at a dosage of 1 mg/kg/day. In all cases, the acne conglobata cleared up completely. With the exception of symptoms produced by drying of mucosa and skin, no side effects were observed. The laboratory parameters were all within normal limits during the anti-acne treatment phase and there was no recurrence of the disease within a period of one year after cessation of treatment. (28)

In another study, the efficacy of isotretinoin was investigated at 0.5 to 1.0 mg/kg per day in the treatment of acne. A number of 638 patients, both male and female, with moderate acne were enrolled and treated with isotretinoin at 20 mg/day for 6 months. At the end of the treatment phase, good results were observed in 94.8% of the patients aged 12 to 20 years, and in 92.6% of the patients aged 21 to 35 years. Failure of the treatment occurred in 5.2% and 7.4% of the two groups, respectively, and twenty-one patients dropped out of thedue to because of side effects. In summary, it can be concluded that six months of treatment with low-dose isotretinoin (20 mg/day) was found to be effective in the treatment of moderate acne, with a low incidence of severe side effects and at a lower cost than higher doses. (29)

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any

subgroup of the target population, for the treatment of severe forms of acne, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Serious damage to an unborn baby *[Teratogenicity]*	Isotretinoin Difa Cooper is teratogenic. That means it is likely to damage an unborn baby. There is also an increased risk of miscarriage. These miscarriages include for example the central nervous system, cardiovascular abnormalities and cleft palate. There is also an increased incidence of spontaneous abortion. The percentage of malformations is high even if isotretinoin was taken only for a short period during pregnancy or when you get pregnant within 5 weeks following the end of treatment. Prescriptions are limited to 30 days treatment for women of childbearing potential. Continuation of treatment requires a new prescription, and each prescription is only valid for seven days. Treatment with Isotretinoin Difa Cooper does not appear to damage sperm. Isotretinoin and its metabolites are present in very low levels in your semen. These levels are considered too low to harm the unborn baby of your female partner. Passage of isotretinoin into human milk is very likely and may	Do not take isotretinoin if you are breastfeeding. You should only take isotretinoin if all the conditions of the Pregnancy Prevention Programme are met (see section "Take special care with Isotretinoin Difa Cooper". Please talk about these issues with your doctor. You must not take Isotretinoin Difa Cooper if you are pregnant or may become pregnant at any time during treatment and for one month after treatment has stopped. If you are a girl or women of child bearing age you can only receive Isotretinoin Difa Cooper treatment if: • you have severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) which has not got better after other anti-acne treatments, including oral antibiotics. • your doctor has explained the teratogenic risk of isotretinoin, and you understand why you must not get pregnant and how to prevent pregnancy. •You are using effective birth control (contraception) without interruption: 1. your doctor will discuss this with

Risk	What is known	Preventability
	harm the baby.	you and give you information on pregnancy prevention including a brochure on contraception explaining the different methods. He or she may refer you to a specialist for contraceptive advice. 2. you must agree to use at least one and preferably two effective methods of contraception including a barrier method (i.e. the pill and condoms) for one month before Isotretinoin Difa Cooper treatment, during treatment and for one month after treatment ends. Before you start treatment your doctor will ask you to take a pregnancy test which must be negative. 3. you must use contraception even if you do not have periods or are not currently sexually active, unless your doctor decides this is not necessary. • you accept that a medically supervised pregnancy test would be performed in the first 3 days of your menstrual cycle prior to starting therapy. If you have unregular menses, the timing of this pregnancy test should reflect your sexual activity and should be undertaken approximately 3 weeks after you had unprotected sexual intercourse. • you understand and accept the need for monthly follow up visits and maybe further pregnancy tests as decided by your doctor. You may then have a pregnancy test 5 weeks after stopping your therapy with Isotretinoin Difa Cooper. You

Risk	What is known	Preventability
		must not become pregnant at any time during treatment or for one month after treatment ends. • your doctor may ask you (or your guardian) to sign an acknowledgment form where you confirm that you have been informed about the risks of Isotretinoin Difa Cooper treatment and that you accept the necessary precautionary measures. If you become pregnant while on Isotretinoin Difa Cooper therapy or during the month after treatment has stopped, immediately stop taking the medicine and contact your doctor. He or she may refer you to a specialist for evaluation and advice. Written information on this subject is available from your doctor. If you haven't received this material please contact your doctor. Prescriptions are limited to 30 days treatment for women of childbearing potential. Each prescription is only valid for seven days.
Psychiatric problems *[Psychiatric disorders including depression, suicidality and anxiety]*	Depression, worsening of depression, aggressive behaviour, anxiety, mood alterations are rare effects (affects 1 to 10 users in 10,000) in patients taking isotretinoin. Abnormal behaviour, psychotic disorder, suicidal thoughts, suicidal attempt, suicide are common effects (affects less than 1 user in 10,000) in patients taking isotretinoin.	Contact the doctor if you have any kind of mental problems, or, if you think you have signs of depression while taking Isotretinoin Difa Cooper such as feeling very sad for no reason, crying spells, difficulty concentrating or you become withdrawn from your friends or family. Your doctor may refer you for appropriate treatment if necessary. Stopping therapy with Isotretinoin Difa Cooper may not be

Risk	What is known	Preventability
		enough and you may require further psychiatric or psychological help.
Eye problems *[Eye disorders including corneal opacities, reduced night vision and keratitis]*	Isotretinoin Difa Cooper therapy may affect your night vision. You may develop dry eyes or sight problems during Isotretinoin Difa Cooper therapy which normally returns to normal once treatment is stopped. Inflammation of the eyelid area, inflammation of the eye, dry eye, eye irritation are very common effects (affects more than 1 user in 10) in patients taking isotretinoin. Blurred vision, clouding of the surface of the eye (cataract), colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, oedema of the optic disk (papilloedema, as sign of benign intracranial hypertension), intolerance to light, visual disturbances are very rare effects (affects less than 1 user in 10,000) in patients taking isotretinoin.	Always be cautious when driving or operating machinery at night because these sight changes can happen quite suddenly. If you wear contact lenses and experience dry eyes you may need to wear glasses for the duration of Isotretinoin Difa Cooper treatment. If you experience any problems with your sight, please inform your doctor immediately, as your Isotretinoin Difa Cooper may need to be stopped and your sight monitored.
Problems in bones and muscles *[Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis]*	Joint pain, muscle pain, back pain (particularly in children and adolescent patients) are very common effects (affects more than 1 user in 10) in patients taking isotretinoin. Inflammation of joint, calcifications in soft tissues (ligaments and tendons), prematurely ending of growing bones, formation of excessive bony tissue	Reduce intensive physical activity during Isotretinoin Difa Cooper therapy, because muscle and joint pain have been observed during Isotretinoin Difa Cooper treatment. Patients are generally advised to contact their doctor or pharmacist if any side effect occurs. They can also report their side effects directly.

Risk	What is known	Preventability
	(exostosis/hypertosis), reduced bone density, tendonitis, muscle breakdown (rhabdomyolysis) are very rare effects (affects less than 1 user in 10,000) in patients taking isotretinoin.	By close monitoring of these side effects the responsible person at the marketing authorization holder gets an indication on whether the product information needs to be updated accordingly.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Gastrointestinal disorders *[Gastrointestinal disorders including inflammatory bowel disease]*	Stop treatment immediately and contact your doctor as soon as possible if you experience severe haemorrhagic diarrhoea (e.g. blood in your stool). Isotretinoin Difa Cooper has on very rare occasions been associated with inflammatory bowel disease. Inflammation of the colon mucosa and intestinal mucosa, gastric and intestinal bleeding, haemorrhagic diarrhoea and inflammatory bowel disease are very rare effects (affects less than 1 user in 10,000) in patients taking isotretinoin.
Use in patients with other diseases and taking other medicines *[Use in high risk patients (including those with diabetes mellitus, obesity, hypervitaminosis A, alcohol abuse, lipid disorders or those also receiving tetracyclines)]*	Isotretinoin Difa Cooper may increase the levels of fats such as triglycerides or cholesterol in your blood. Your doctor will do some blood tests in order to monitor these levels before, during and at the end of your Isotretinoin Difa Cooper treatment. Tell your doctor if you already have high levels of these substances in your blood or if you have diabetes, are overweight, or are an alcoholic, as you may need to get the blood tests more frequently. Isotretinoin Difa Cooper may increase your blood sugar levels and in rare cases diabetes mellitus has been diagnosed. Your doctor may monitor your blood sugar levels during your treatment, particularly if you have diabetes, are overweight, or are an alcoholic. Do not take vitamin A supplements or tetracyclines (a type of antibiotic) during therapy with Isotretinoin Difa Cooper because the risk of getting side effects may increase. Blood levels of fat-like substances (triglyceride) increased, HDL-cholesterol (high density lipoprotein) decreased are very common effects (affects more than 1 user in 10) in patients taking isotretinoin. Blood cholesterol increased, blood sugar levels (blood glucose) increased, blood in the urine, excretion of protein in the urine are common effects (affects 1 to 10 users in 100) in patients taking

Risk	What is known (Including reason why it is considered a potential risk)
	isotretinoin.

Missing information

None proposed.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

For this medicinal product additional risk minimisation measures are implemented and refer to the following risk:

Isotretinoin is <u>teratogenic.</u>

That means it is likely to damage an unborn baby. There is also an increased risk of miscarriage. These miscarriages include for example the central nervous system, cardiovascular abnormalities and cleft palate. There is also an increased incidence of spontaneous abortion. The percentage of malformations is high even if isotretinoin was taken only for a short period during pregnancy or when you get pregnant within 5 weeks following the end of treatment.

- **Risk minimisation measure:**
  Distribution of educational material to Healthcare Professional, pharmacists and patients

<u>Objective and rationale</u>

Patients and Health Care Professionals should understand the risk of damage to the unborn baby, and the increased risk of miscarriage and spontaneous abortion if pregnancy occurs under isotretinoin treatment or within 5 weeks after the end of treatment.

<u>Proposed action:</u>

Educational materials (agreed with the Agencies on national level) to be provided to prescribing physicians, patients and pharmacists including advice:

- Brochure for pharmacists
- Brochure for dermatologists
- Brochure for female patients on pregnancy prevention methods
- Check-list for the dermatologist
- Declaration of consents

- **Risk minimisation measure:**
  Prescribing and dispensing restrictions

• **Risk minimisation measure:** Prescribing and dispensing restrictions
Objective and rationale Patients and Health Care Professionals should understand the risk of damage to the unborn baby, and the increased risk of miscarriage and spontaneous abortion if pregnancy occurs under isotretinoin treatment or within 5 weeks after the end of treatment. Proposed action: Prescriptions of isotretinoin for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

• **Risk minimisation measure:** Warnings in the Summary of Product Characteristics and the Package Leaflet
Objective and rationale Patients and HCPs to understand the risk of damage to the unborn bay, miscarriage and spontaneous abortion if pregnancy occurs under isotretinoin or within 5 weeks after the end of treatment. Proposed action: Warnings in the Summary of Product Characteristics (directed to the prescriber) and the Package Leaflet (directed to the patient) on how to avoid pregnancy during isotretinoin therapy and within 5 weeks after finalisation of the therapy.

VI.2.6 Planned post authorisation development plan

No additional studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.