PRODUCT MONOGRAPH

HANZEMA™

Alitretinoin Capsules
10 mg and 30 mg

Immunomodulator/Anti-inflammatory agent

DIN Owner:
Dr. Reddy's Laboratories, Inc.
Princeton, NJ – 08540 USA

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule/ 10 mg	DL-α-tocopherol, Gelatin, Glycerin, Medium chain triglycerides, Glyceryl distearate, Glyceryl Monooleate, Non crystallising sorbitol solution, Soybean oil, Water, iron oxide red, iron oxide black. The imprinting Opacode® S-1-7085 white contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.
Oral	Capsule/ 30 mg	DL-α-tocopherol, Gelatin, Glycerin, Medium chain triglycerides, Glyceryl distearate, Glyceryl Monooleate, Sorbitol, Soybean oil, Water, iron oxide red, iron oxide yellow. The imprinting Opacode® S-1-7085 white contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

INDICATIONS AND CLINICAL USE

HANZEMA (alitretinoin) is indicated for the treatment of severe chronic hand eczema refractory to high potency topical corticosteroids in adults.

HANZEMA should only be prescribed by physicians knowledgeable in the use and monitoring requirements of systemic retinoids, who understand the risk of teratogenicity in females of child bearing potential (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions and Special Populations, Women of Child Bearing Potential**).

Geriatrics (> 65 years of age):
Clinical trial experience has not identified differences in responses between elderly and other patients. However clinical studies of alitretinoin did not include sufficient numbers of subjects aged 65 years and over to determine with certainty whether they respond differently from younger subjects (ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pharmacokinetics

in special populations).

Pediatrics (< 18 years of age):

HANZEMA is not recommended for use in patients under 18 years of age.

CONTRAINDICATIONS

HANZEMA (alitretinoin) is contraindicated in pregnancy.

Females must not become pregnant while taking HANZEMA and for at least one month after its discontinuation. HANZEMA can cause severe birth defects in infants born to women who become pregnant during treatment with HANZEMA in any amount, even for a short period of time. Potentially any exposed fetus can be affected. There are no accurate means of determining whether an exposed fetus has been affected (see **WARNINGS AND PRECAUTIONS: Special populations, Women of child bearing potential**).

If pregnancy does occur during treatment with HANZEMA or within one month after its discontinuation, HANZEMA treatment must be immediately stopped and a physician and the patient should discuss the desirability of continuing the pregnancy.

HANZEMA should only be prescribed by physicians knowledgeable in the use of systemic retinoids, who have full understanding of the risks of systemic retinoid therapy and the monitoring requirements (see **INDICATIONS AND CLINICAL USE**).

HANZEMA is contraindicated in females of childbearing potential unless all of the conditions of the Pregnancy Prevention Program are met (see **WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program for women of childbearing potential**).

HANZEMA is contraindicated in breastfeeding women.

HANZEMA is also contraindicated in patients:

- With hepatic insufficiency
- With severe renal insufficiency
- With uncontrolled hypercholesterolemia
- With uncontrolled hypertriglyceridemia
- With uncontrolled hypothyroidism
- With hypervitaminosis A
- With hypersensitivity either to alitretinoin, to other retinoids or to any of the excipients, in particular in case of allergies to peanut or soya. For a complete listing see the Dosage Forms, Composition and Packaging section of the product monograph.

- With rare hereditary problems of fructose intolerance

- Receiving concomitant treatment with tetracyclines (see **WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS**)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Pregnancy Prevention: HANZEMA (alitretinoin) is a known teratogen contraindicated in pregnancy (see **boxed CONTRAINDICATIONS**). Physicians should **only** prescribe HANZEMA to females of childbearing potential if **ALL** the conditions described below under **Pregnancy Prevention Program for women of childbearing potential** are met.

In addition, when prescribing this drug to female patients of childbearing potential, physicians **must** use the HANZEMA Pregnancy Prevention Program, which includes comprehensive information about the potential risks of this drug, a checklist for criteria which **must** be met prior to prescribing this drug to female patients of childbearing potential, detailed information on birth control options, a patient acknowledgement form for review and signature, and monthly pregnancy reminders for physicians to use at each patient visit during the treatment period.

Neurologic: Treatment with systemic retinoids, including alitretinoin, has been associated with the occurrence of benign intracranial hypertension, some of which involved concomitant use of tetracyclines (see **CONTRAINDICATIONS and DRUG INTERACTIONS**). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop signs of benign intracranial hypertension should discontinue alitretinoin immediately (class effect).

In the event of relapse treatment, the patient must also use the same uninterrupted and effective contraceptive measures one month prior to, during and for one month after HANZEMA and fulfill all the same requirements prior to treatment.

Pregnancy Prevention Program for women of childbearing potential

This medicinal product is TERATOGENIC.

HANZEMA is contraindicated in a woman of childbearing potential unless she understands the teratogenic risk and agrees to comply with all of the following conditions of the Pregnancy Prevention Program:

Before starting treatment the patient must:
- read the "Patient Guide"
- read and sign the "Acknowledgement Form for HANZEMA Patients"

For one month before treatment, during treatment and for one month after treatment the patient must:

- use two effective and complementary forms of contraception without interruption including a barrier method (see **Special Populations, Women of childbearing potential, Contraception**)
- rapidly consult a doctor if there is a risk of pregnancy
- undergo medically supervised, monthly pregnancy testing (see **Special Populations, Women of childbearing potential, Pregnancy Tests**)

Before prescribing HANZEMA the physician must:

- ensure that the patient has used two methods of effective and complementary contraception for at least one month prior to initiating HANZEMA (see **Special Populations, Women of childbearing potential, Contraception**)
- perform two separate pregnancy tests (see **Special Populations, Women of childbearing potential, Pregnancy Tests**)
- retain the signed "Acknowledgement Form for HANZEMA Patients"

During treatment with HANZEMA the physician must:

- see the patient monthly to ensure contraception compliance and perform pregnancy testing, before prescribing HANZEMA again
- ensure any pregnancies and their outcomes are reported to DRL by fax at: 1-855-681-1280 or by email at: druginfo@drreddys.com

Special Populations

1. Women of child bearing potential:

There is an extremely high risk that major human fetal abnormalities will occur if pregnancy occurs during treatment with HANZEMA or up to one month following its discontinuation. Potentially any exposed fetus can be affected.

- **Pregnancy Tests:** Female patients of childbearing potential must not be given HANZEMA until pregnancy is excluded.

One month prior to starting therapy:
The patient must have two negative pregnancy tests with a sensitivity of at least 25 mIU/mL, performed at least 3 weeks apart, before starting HANZEMA therapy.
The first medically supervised pregnancy test should be conducted in the first 3 days of the menstrual cycle and its date and results recorded. When the patient is qualified for HANZEMA therapy by the physician after one month of contraceptive use, a second serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL performed in a licensed laboratory, must be performed within 11 days prior to starting HANZEMA treatment.

At the start of therapy:
HANZEMA treatment should start on the second or third day of the next normal menstrual period following the second negative pregnancy test.

Follow-up visits:
During treatment, it is mandatory that all female patients of childbearing potential treated with HANZEMA have regular monthly pregnancy tests before being prescribed HANZEMA again.

End of treatment:
Patients must undergo a medically supervised pregnancy test one month after the discontinuation of treatment. The dates and results of pregnancy tests should be documented.

These pregnancy tests will:

- Serve primarily to reinforce to the patient the necessity of avoiding pregnancy.
- In the event of accidental pregnancy, provide the physician and patient an immediate opportunity to discuss the serious risk to the fetus from this exposure to alitretinoin and the desirability of continuing the pregnancy in view of the potential teratogenic effect of HANZEMA (see **CONTRAINDICATIONS and TOXICOLOGY: Reproduction and Teratology Studies**).

- **Contraception:** Effective contraception must be used for at least one month before starting HANZEMA treatment, during treatment and for at least one month following the discontinuation of HANZEMA treatment. Two effective and complementary forms of contraception must be used simultaneously. At least one of these forms of contraception must be a primary form, unless the patient has undergone a hysterectomy. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective and complementary forms of contraception simultaneously. Microdosed progesterone preparations (minipills) are not a suitable method of contraception during HANZEMA therapy (see **DRUG INTERACTIONS; Drug-Drug Interactions**).

Contraception must be used unless permanent infertility has been medically diagnosed. Even female patients who claim absence of sexual activity must be advised to employ contraception while taking HANZEMA, following the above guidelines.

Contraception must be used for at least one month after stopping treatment with HANZEMA, even in patients with amenorrhea.

Effective forms of contraception:

Primary methods*	**Secondary methods***
• Tubal sterilisation • Partner's vasectomy • Intrauterine device (IUD) • Hormonal (combination oral contraceptives, transdermal patch, injectables, or vaginal ring)	• Male condom with or without spermicide • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge (contains spermicide)

*Progestogen-only contraceptives ("mini-pills") and female condoms are inadequate methods of contraception for use with HANZEMA.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

Pregnancy: Pregnancy is an absolute contraindication to treatment with HANZEMA (see **CONTRAINDICATIONS**).

HANZEMA is a retinoid and therefore is a potent teratogen. Pregnancy occurring during treatment with HANZEMA and for one month after its discontinuation, carries the risk of fetal malformation and the increased risk of spontaneous abortion (see **CONTRAINDICATIONS and TOXICOLOGY: Reproduction and Teratology Studies**). The fetal malformations associated with exposure to retinoids include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities.

HANZEMA treatment must be stopped and the patient should be fully counselled regarding the serious risk to the fetus should they become pregnant while undergoing treatment. If pregnancy does occur during this time the physician and patient should discuss the desirability of continuing the pregnancy.

- **Breastfeeding Women*:*** Alitretinoin is highly lipophilic, therefore the passage of alitretinoin into human milk is very likely. Due to the potential risk for the exposed child, the use of HANZEMA is contraindicated in breast feeding mothers (see **CONTRAINDICATIONS**).

Pregnancy Prevention Program materials can be obtained from Dr. Reddy's Laboratories Canada Inc. through the toll free telephone number at Tel: 1-855-845-1739 or through the www.drreddys.com website.

Prescribing and dispensing restrictions

Prescriptions of HANZEMA for women of childbearing potential must be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, review of pregnancy test results, issuing a prescription and dispensing of HANZEMA should occur on the same day. Dispensing of HANZEMA must be completed within 7 days of the medically supervised pregnancy test.

2. Male patients

Small amounts of alitretinoin (above endogenous levels) have been detected in the semen of some healthy volunteers receiving 40 mg of alitretinoin. Drug accumulation in semen is not expected.
Assuming complete vaginal absorption, these amounts would have a negligible effect on the endogenous plasma levels of the female partner or a fetus and therefore do not appear to pose a

risk to the fetus if the partner is pregnant. Based on non-clinical findings, the male fertility may be compromised by treatment with alitretinoin.

General

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

HANZEMA should not be prescribed if the patient's eczema (dermatitis) can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids.

All patients should be reminded never to give this medicinal product to another person, particularly not to females, and to return any unused capsules to their pharmacist at the end of treatment.

Blood Donations: Patients should not donate blood during therapy and for one month following discontinuation of HANZEMA because of the potential risk to the fetus of a pregnant transfusion recipient.

Carcinogenesis and Mutagenesis

Alitretinoin was tested in 2-year carcinogenicity studies in rats and mice. Dose-related retinoid-specific toxicity was seen at higher doses, but no carcinogenic potential was noted (see **TOXICOLOGY, Carcinogenicity**).

Cardiovascular/Lipid Metabolism

Alitretinoin has been associated with an increase in plasma cholesterol and triglyceride levels.

Patients with increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake and familial history.

The cardiovascular consequences of hypertriglyceridemia are not well understood, but may increase the patient's risk status. Therefore, serum cholesterol and triglycerides (fasting values) should be monitored.

HANZEMA should be discontinued if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. Triglyceride levels in excess of 800mg/dL (9mmol/L) are sometimes associated with acute pancreatitis, which may be fatal.

Patients at high risk for cardiac events should be carefully monitored due to increases in lipid levels.

In patients with diabetes, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with HANZEMA, more frequent checks of serum values for lipids and/or blood glucose may be necessary.

Endocrine and Metabolism

Changes in thyroid function tests have been observed in patients receiving alitretinoin, most often noted as a reversible reduction in thyroid stimulating hormone (TSH) levels and T4 [free

thyroxine].

Gastrointestinal

Systemic retinoids, including HANZEMA, have been associated with inflammatory bowel disease (IBD), including regional ileitis, in patients without a history of intestinal disorders. If severe diarrhea is observed diagnosis of IBD should be considered. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue HANZEMA immediately.

Hepatic/Biliary/Pancreatic

Treatment with systemic retinoids, including HANZEMA, has been associated with transient and reversible increases in liver transaminases. In the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

There have been some reports of acute pancreatitis, which is known to be potentially fatal. This is sometimes associated with elevation of serum triglycerides in excess of 800 mg/dL or 9 mmol/L (see **ADVERSE REACTIONS**). Therefore, every attempt should be made to control significant triglyceride elevation (see **WARNINGS AND PRECAUTIONS: Cardiovascular/Lipid Metabolism**). HANZEMA should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Immune

Anaphylactic reactions have been rarely reported in systemic retinoids, including HANZEMA, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Musculo-skeletal and connective tissue disorders

Treatment with other systemic retinoids has been associated with bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments.

Myalgia, arthralgia and increased serum creatinine phosphokinase values have been observed in patients treated with alitretinoin.

Neurologic

Treatment with systemic retinoids, including HANZEMA, has been associated with the occurrence of benign intracranial hypertension, some of which involved concomitant use of tetracyclines (see **CONTRAINDICATIONS and DRUG INTERACTIONS**). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop signs of benign intracranial hypertension should discontinue HANZEMA immediately.

Ophthalmologic

Treatment with HANZEMA has been associated with dry eyes. The symptoms usually resolve

after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Treatment with systemic retinoids has been associated with corneal opacities, keratitis and conjunctivitis. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored (see **ADVERSE REACTIONS: Clinical Trial and Post-Market Adverse Drug Reactions**).

Decreased night vision has been reported in patients treated with alitretinoin and other retinoids. These effects usually resolve after discontinuation of therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Patients experiencing visual difficulties should be referred to an ophthalmologist. Withdrawal of alitretinoin may be necessary.

Psychiatric

Depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with systemic retinoids including alitretinoin. Particular care needs to be taken in patients with a history of depression and patients on HANZEMA treatment should therefore be observed for signs of depression and referred for appropriate treatment if necessary. Therefore, prior to initiation of HANZEMA and at each visit during therapy, patients should be asked about any psychiatric disorder, depression, or mood disturbance. Patients should stop HANZEMA if they develop depression, mood disturbance, psychosis, or aggression. Patients should be monitored until new symptoms resolve. Awareness by family or friends may be useful to detect mental health deterioration. However, discontinuation of HANZEMA may be insufficient to alleviate symptoms and therefore further psychiatricor psychological evaluation may be necessary.

Skin

The effects of UV light are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and the unsupervised use of sun lamps. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Patients who experience dryness of the skin and lips should be advised to use a skin moisturizing ointment or cream and a lip balm.

Monitoring and Laboratory Tests

Pregnancy tests: The patient should have two negative pregnancy tests (β-hCG in urine or serum) with a sensitivity of at least 25 mIU/mL before starting HANZEMA therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for HANZEMA therapy by the physician. The patient then should have a second pregnancy test with a sensitivity of at least 25 mIU/mL with a negative result, performed in a licensed laboratory, within 11 days prior to initiating therapy. The patient **must wait until the second or third day of their next normal menstrual period before starting HANZEMA.**

Pregnancy testing must be repeated monthly for pregnancy detection during Hanzema treatment and at one month after discontinuation of treatment. The dates and results of the pregnancy tests should be documented.

The following tests are required before starting HANZEMA, at first month, then as clinically indicated:

- Serum blood lipid determinations (under fasting conditions) should be performed before HANZEMA is given and then at intervals (one month after the start of therapy) until the lipid response to HANZEMA is established (which usually occurs within four weeks), and also at the end of treatment. (See **WARNINGS AND PRECAUTIONS; General; Cardiovascular/Lipid Metabolism**)

- Blood glucose level: patients with known or suspected diabetes should have periodic blood sugar determinations.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In blinded studies, 1382 patients with CHE received alitretinoin (1101 patients) or placebo (281 patients). Of these, 426 patients received alitretinoin at 30 mg per day (182 for ≥ 24 weeks) and 514 received 10 mg per day (240 for ≥ 24 weeks). The most frequent adverse drug reaction (ADR) observed under alitretinoin therapy are headache (30mg: 21.6%; 10mg: 11.3%), flushing (30mg: 5.9%, 10mg: 1.6%), erythema (30mg: 7.3%,10mg: 1.6%) and dry lip (30mg: 5.6%, 10mg: 3.7%).

In study BAP00089, the percentage of patients who discontinued therapy due to adverse events was: 9.3% (30 mg), 5.3% (10 mg) and 5.4% (placebo). The most common reason for discontinuation was headache (4.1% 30 mg, 1.4% 10 mg, 0.5% placebo), which typically occurred within the first 10 days of therapy, and was transient. These reversible ADRs are dose dependent and may therefore be alleviated by dose reduction.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by ≥ 1% of Patients in Any Treatment Group: Blinded Patient Studies Population (Studies BAP00003, BAP00089 and BAP00200)

	Alitretinoin 30mg	Alitretinoin 10mg	Placebo
Number of Patients in Safety Population	426 (100.0%)	514 (100.0%)	281 (100.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
ECZEMA	15 (3.5%)	18 (3.5%)	11 (3.9%)
ERYTHEMA	31 (7.3%)	8 (1.6%)	4 (1.4%)
DRY SKIN*	12 (2.8%)	14 (2.7%)	3 (1.1%)
DERMATITIS	7 (1.6%)	7 (1.4%)	5 (1.8%)
PRURITUS	6 (1.4%)	5 (1.0%)	5 (1.8%)
RASH	4 (0.9%)	6 (1.2%)	4 (1.4%)
ALOPECIA*	7 (1.6%)	0	0
NERVOUS SYSTEM DISORDER			
HEADACHE*	92 (21.6%)	58 (11.3%)	22 (7.8%)
DIZZINESS	3 (0.7%)	9 (1.8%)	3 (1.1%)
INFECTIONS AND INFESTATIONS			
NASOPHARYNGITIS	26 (6.1%)	26 (5.1%)	14 (5.0%)
INFLUENZA	6 (1.4%)	11 (2.1%)	4 (1.4%)
UPPER RESPIRATORY TRACT INFECTION	9 (2.1%)	5 (1.0%)	5 (1.8%)
PHARYNGITIS	6 (1.4%)	5 (1.0%)	1 (0.4%)
HERPES SIMPLEX	5 (1.2%)	1 (0.2%)	3 (1.1%)
RHINITIS	3 (0.7%)	2 (0.4%)	4 (1.4%)
FOLLICULITIS	0	2 (0.4%)	3 (1.1%)
GASTROINTESTINAL DISORDERS			
LIP DRY*	24 (5.6%)	19 (3.7%)	9 (3.2%)
DRY MOUTH*	12 (2.8%)	13 (2.5%)	3 (1.1%)
NAUSEA	14 (3.3%)	12 (2.3%)	5 (1.8%)
CHEILITIS	7 (1.6%)	6 (1.2%)	1 (0.4%)
DIARRHOEA	4 (0.9%)	7 (1.4%)	4 (1.4%)
ABDOMINAL PAIN UPPER	5 (1.2%)	4 (0.8%)	1 (0.4%)
VOMITING	5 (1.2%)	3 (0.6%)	1 (0.4%)
DYSPEPSIA	6 (1.4%)	2 (0.4%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
BACK PAIN	6 (1.4%)	11 (2.1%)	3 (1.1%)
ARTHRALGIA	8 (1.9%)	5 (1.0%)	3 (1.1%)
MYALGIA	5 (1.2%)	4 (0.8%)	3 (1.1%)
PAIN IN EXTREMITY	1 (0.2%)	6 (1.2%)	4 (1.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
FATIGUE	9 (2.1%)	10 (1.9%)	5 (1.8%)
EYE DISORDERS			
CONJUNCTIVITIS*	8 (1.9%)	6 (1.2%)	3 (1.1%)
DRY EYE*	11 (2.6%)	9 (1.8%)	1 (0.4%)
ABNORMAL EYE SENSATION	5 (1.2%)	1 (0.2%)	0
INVESTIGATIONS			
BLOOD CREATINE PHOSPHOKINASE INC.	13 (3.1%)	8 (1.6%)	4 (1.4%)
BLOOD TRIGLYCERIDES INCREASED	12 (2.8%)	3 (0.6%)	0
WEIGHT INCREASED	5 (1.2%)	4 (0.8%)	2 (0.7%)
VASCULAR DISORDERS			
FLUSHING	25 (5.9%)	8 (1.6%)	3 (1.1%)
HYPERTENSION	7 (1.6%)	6 (1.2%)	1 (0.4%)
HOT FLUSH	5 (1.2%)	2 (0.4%)	1 (0.4%)
PSYCHIATRIC DISORDERS			
DEPRESSION*	11 (2.6%)	9 (1.8%)	5 (1.8%)
INSOMNIA	3 (0.7%)	5 (1.0%)	3 (1.1%)
SLEEP DISORDER	3 (0.7%)	1 (0.2%)	3 (1.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
PHARYNGOLARYNGEAL PAIN	5 (1.2%)	5 (1.0%)	3 (1.1%)
METABOLISM AND NUTRITION DISORDERS			
HYPERCHOLESTEROLAEMIA	5 (1.2%)	3 (0.6%)	1 (0.4%)

*similar Medra terms were combined in this calculation

Headache was the most common adverse event (AE) and clearly showed a dose effect. Erythema and dry lips were also more frequent with alitretinoin 30 mg than with alitretinoin 10 mg. Additional AEs occurring with highest incidence in the 30 mg alitretinoin arm included dry skin, conjunctivitis, hypercholesterolemia, and flushing. Other commonly occurring AEs without strong apparent dose effect included nasopharyngitis, and eczema. All other treatment-emergent AEs were of similar frequency in the two alitretinoin groups and with the placebo group.

Psychiatric effects, in particular depression, and mood changes and suicidal ideation, have been associated with retinoids including alitretinoin. In alitretinoin clinical studies, patients have been monitored for depression using the CES-D (Center for Epidemiological Studies-Depression) score. Treatment with alitretinoin was not associated with changes in the CES-D score.

The following adverse events were not observed in clinical trials with alitretinoin, but have been observed with other retinoids: diabetes mellitus, color blindness (color vision deficiencies), and contact lens intolerance.

Changes in bone mineralization and extra-osseous calcifications have been associated with systemic retinoid treatment. In clinical studies with alitretinoin, degenerative changes of the spine and ligamentous calcifications were frequent findings in patients with chronic hand eczema before treatment (baseline), with minor progression in a small number of patients during treatment. These observations were consistent with age dependent degenerative changes. Assessments of bone density (DXA) did not indicate a dose dependent effect on bone mineralization.

The most common laboratory changes consisted of increased levels of triglycerides (30mg: 35.4%; 10mg: 17.0%), increased cholesterol (30mg: 27.8%; 10mg 16.7%), decreased levels of thyroid stimulating hormone (TSH, 30mg: 8.4%, 10mg: 6.0%) and decreased levels of free T4 (30mg: 10.5%; 10mg: 2.9%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Nervous system disorders: Benign intracranial hypertension
Eye disorders: Blurred vision, cataract
Vascular disorders: Vasculitis
Respiratory, thoracic and mediastinal disorders: Epistaxis
Skin and subcutaneous tissues disorders: Pruritus, rash, skin exfoliation, asteatotic eczema
Musculo-skeletal and connective tissue disorders: exostosis, (hyperostosis), ankylosing spondylitis

Abnormal Hematologic and Clinical Chemistry Findings

The most frequent and relevant changes in individual laboratory values included elevated levels of fasting cholesterol and triglycerides with corresponding changes in high density lipoproteins (HDL) and low density lipoproteins (LDL), and lowered levels of thyroxin and TSH, predominantly in the 30 mg dose group. Other frequently reported changes were reductions in hemoglobin, hematocrit, and red blood cell (RBC) counts, which were more frequent in the 30 mg dose group. Elevated levels of creatinine phosphokinase were frequent in both alitretinoin groups. Decreased monocytes were more frequently observed in the active treatment groups

compared to placebo (30 mg, 10 mg, placebo: 22.1%, 16.3% and 8%, respectively) (See Table 2).

Table 2 Abnormal Hematologic and Clinical Chemistry Findings

	30 mg	**10 mg**	**Placebo**
Number of Patients in Safety population	410	418	203
>10% of patients outside marked reference range	LDL calculated high	LDL calculated high	
5-10% of patients outside marked reference range	Total cholesterol high Triglycerides high HDL low		
1-5% of patients outside marked reference range	Iron low, Total iron binding capacity high; Neutrophils absolute count low; Eosinophils high; Creatinine kinase high; Low density lipoproteins high; Thyroid stimulating hormone low	Reticulocyte count low; Eosinophils high Creatinine kinase high HDL low TSH low	Leucocytes high; Lymphocytes absolute count high; Neutrophils absolute count low; Eosinophils high; Creatinine kinase high, Total cholesterol high HDL low; LDL calculated high Thyroid stimulating hormone low

Post-Market Adverse Drug Reactions

In addition to the ADRs listed above, there have also been post marketing reports of the following ADRs:

Blood and lymphatic system disorders: Thrombocytes increased (thrombocytosis)
Ear and labyrinth disorders: Tinnitus
Eye disorders: Decreased night vision (night blindness), eye irritation
Gastrointestinal disorders: Inflammatory bowel disease
General disorders and administration site conditions: Peripheral oedema
Hepatobiliary disorders: Transaminase increased
Immune system disorders: Anaphylactic reactions, hypersensitivity
Skin and subcutaneous tissue disorders: Nail disorders, photosensitivity reaction

DRUG INTERACTIONS

Overview
Alitretinoin is metabolized by cytochrome P450 (CYP) 2C9, CYP2C8, and CYP3A4 and undergoes isomerisation.

Drug-Drug Interactions

Concomitant medications that may affect the pharmacokinetics of alitretinoin

Table 3 Influence of Concomitant Medications on Alitretinoin Pharmacokinetics and Any Resulting Changes in the Dosing Recommendations of Alitretinoin

Concomitant Medication	Effect of Concomitant Medication on Alitretinoin Pharmacokinetics	Recommendation
Ketoconazole, 200 mg	Ketoconazole increased the C_{max} of alitretinoin by ~50% and 4-oxo-alitretinoin by ~13%; similar increases were seen with AUC	A reduction in dose to 10 mg should be considered when alitretinoin is co-administered with ketoconazole or other potent CYP3A4 inhibitors.
Simvastatin, ciclosporin A	No clinically relevant changes in alitretinoin pharmacokinetics were seen	Co-administration of simvastatin, ciclosporin A, or any medications that inhibit P-glycoprotein, breast cancer resistance protein, or organic anion-transporting polypeptide are not expected to result in clinically relevant changes in the systemic exposure of alitretinoin.
Potent CYP2C9 or CYP2C8 inhibitors	*In vitro* Interaction	A reduction in dose to 10 mg should be considered when alitretinoin is administered with potent CYP2C9 inhibitors (eg, diosmin, fluconazole, miconazole, oxandrolone) or potent CYP2C8 inhibitors (eg, gemfibrozil).

Effect of alitretinoin on the pharmacokinetics of concomitant medications

Table 4 Influence of Alitretinoin on Concomitant Medication Pharmacokinetics and Any Resulting Changes in the Dosing Recommendations of Concomitant Medications

Concomitant Medication	Effect of Alitretinoin on Pharmacokinetics of Concomitant Medication	Conclusion/Recommendation
Ketoconazole, and ciclosporin A	Alitretinoin does not affect exposure of ketoconazole or ciclosporin A	Alitretinoin is not likely to affect the exposure of concomitant medications that are CYP3A4 substrates, including those that are sensitive CYP3A4 substrates
Simvastatin and simvastatin acid	Small (<25%) inconsistent decreases in simvastatin and simvastatin acid exposure were observed when co-administered with alitretinoin	The potential for alitretinoin to inhibit CYP3A4 and breast cancer resistance protein is low

CYP 2C8 substrate	A model based on *in vitro* data predicted that alitretinoin may increase the exposure of CYP2C8 substrates, with a 40% increase in the AUC of cerivastatin (a sensitive probe substrate), consistent with weak inhibition by alitretinoin	Alitretinoin may increase the exposure of CYP2C8 substrates; therefore co-administration with amiodarone (a CYP2C8 substrate with a long half-life and narrow therapeutic index) is not recommended. Caution should be used if alitretinoin is co-administered with other medications that are substrates for CYP2C8 (eg, paclitaxel, rosiglitazone, repaglinide). Monitoring for adverse drug reactions related to the concomitant medication should be considered
CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, P-glycoprotein (P-gp), organic anion-transporting polypeptide 1B1 (OATP1B1), organic anion-transporting polypeptide 1B3 (OATP1B3), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and organic cation transporter 2 (OCT2) substrates	Models based on *in vitro* data predicted that alitretinoin administration does not affect the exposure of concomitant medications that are substrates for these enzymes	Alitretinoin administration is not likely to affect the exposure of concomitant medications that are substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2

Microdosed progesterone preparations (minipills) are not a suitable method of contraception during HANZEMA therapy.

An increased risk of liver toxicity may be seen if retinoids are taken concomitantly with methotrexate.

Interactions Related to Hormonal Contraception

Because effective contraception is imperative in women of child-bearing potential receiving alitretinoin; medications known to be potent inducers of metabolism (e.g. St John's Wort, some anti-epileptics and protease inhibitors) should not be co-administered with alitretinoin in women who take hormonal contraceptives, as contraceptive effectiveness may be reduced. Prescribers are advised to consult the prescribing information of any medication including non-prescription medication or herbal medicine co-administered with hormonal contraceptives.

No drug interactions were observed when alitretinoin was co-administered with the oral contraceptive ethinyl estradiol and norgestimate.

Pharmacodynamic Interactions

Patients should not take vitamin A or other retinoids as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with

concomitant use of retinoids and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see **CONTRAINDICATIONS and Serious Warnings and Precautions**).

Drug-Food Interactions

A clinical pharmacology study with an early formulation of alitretinoin demonstrated that when alitretinoin is taken with a high-fat meal, the systemic exposure is considerably enhanced. All subsequent clinical studies were done in a fed state with various formulations. Therefore, HANZEMA should be administered with a main meal once daily, preferably at the same time of day to maximize exposure (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dose for HANZEMA is 10 mg or 30 mg once daily, preferably at the same time each day, with a main meal. The recommended starting dose is 30 mg once daily. Dose reduction to 10 mg once daily may be considered in patients with unacceptable side effects.

Patients at high risk for cardiac events should be carefully monitored due to increases in lipid levels (see **WARNINGS AND PRECAUTIONS, Cardiovascular/Lipid Metabolism**).

In studies investigating 10 mg and 30 mg daily doses, both doses resulted in clearing of the disease. The 30 mg dose provided a more rapid response and a higher response rate. The 10 mg daily dose was associated with fewer adverse events (see **ADVERSE REACTIONS and CLINICAL TRIALS**).

A treatment course of HANZEMA may be given for 12 to 24 weeks depending on response. Discontinuation of therapy is recommended in patients who have achieved clear or almost clear hands earlier than 24 weeks. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of continuous treatment. In the event of relapse, patients may benefit from further treatment courses of HANZEMA.

Pediatrics
HANZEMA is not recommended for use in patients under 18 years of age.

Missed Dose
The missed dose should be taken as soon as it is remembered, and then the regular dosing schedule should be continued. Two doses of HANZEMA should not be taken on the same day.

Administration
The capsules should be taken once daily, preferably at the same time each day, and must be taken with a main meal.

OVERDOSAGE

For management of suspected overdose, contact your regional Poison Control Centre.

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10-fold the therapeutic dosage given for chronic hand eczema. The toxicity observed was consistent with vitamin A toxicity, and included severe headache, diarrhea, facial flushing, hypertriglyceridaemia. These effects were reversible.

The following precautions should be taken with all female patients of childbearing potential who have taken an overdose of HANZEMA:

1. At the time of the overdose, a pregnancy test must be performed.
2. One complete menstrual cycle or one month after the overdose, a second pregnancy test must be performed.
3. Effective contraception must be used for at least one complete menstrual cycle after the overdose. Patients who present with a positive pregnancy test at the time of the overdose, or one complete menstrual cycle / one month after the overdose, should be fully counselled on the serious risk to the fetus from this exposure to HANZEMA and the physician and the patient should discuss the desirability of continuing the pregnancy (See **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations, Women of Child Bearing Potential and TOXICOLOGY: Reproduction and Teratology Studies**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The pharmacological action of retinoids may be explained by their effects on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinization, sebum secretion and immunomodulation. Unlike other retinoids, which are specific agonists of either RAR or RXR receptors, alitretinoin binds to members of both receptor families. The mechanism of action of alitretinoin in chronic hand dermatitis is unknown. Alitretinoin has demonstrated immunomodulatory and anti-inflammatory effects that are relevant to skin inflammation. Alitretinoin suppresses the production of chemokines that are involved in recruitment of leukocytes to sites of skin inflammation, reduces expansion of T lymphocytes and antigen-presenting cells, and inhibits effect on cell differentiation. CXCR3 ligands and CCL20 chemokines, expressed in eczematous skin lesions, are down-regulated by alitretinoin in cytokine-stimulated keratinocytes and dermal endothelial cells. In addition, alitretinoin suppresses the expansion of cytokine activated leucocytes subsets and antigen presenting cells.

It has been observed that in humans alitretinoin only minimally affects sebum secretion.

Pharmacokinetics

Absorption

Alitretinoin is a low solubility, low permeability compound with a low and variable bioavailability. Alitretinoin is not consistently absorbed from the gastrointestinal tract in the

fasted state. The systemic exposure is considerably enhanced when taken with a main meal.

In vitro data from a gastrointestinal system suggest the amount of alitretinoin available for absorption differs with fat intake (when given with an approximately 25% fat meal, the amount available for absorption is less than when given with ~40% or ~60% fat meal). Therefore, alitretinoin should be administered with a main meal once daily, preferably at the same time of day to maximise exposure.

After administration of alitretinoin 30 mg once daily with a main meal , the median T_{max} is 4 hours, the average C_{max} is 177 ng/mL, and the average $AUC_{(0-\tau)}$ is 405 ng*hr/mL. Moderate to large intrasubject and intersubject variability for AUC(0-∞) and C_{max} of alitretinoin after a single and repeat dose was observed.

Peak plasma concentrations (C_{max}) and exposure (AUC) of alitretinoin increase with increasing single doses over the range of 5 to 150 mg. AUC values of alitretinoin increases proportionally with dose for once daily doses of 10 mg to 30 mg. The C_{max} of alitretinoin may increase less than proportionally with increasing dose.

Distribution

Alitretinoin is 99.1% bound to plasma proteins. The volume of distribution of alitretinoin is estimated to be greater than the extracellular volume (>14L), but less than total body water.

Metabolism

Alitretinoin is metabolized by CYP2C9, CYP2C8, and CYP3A4 isoenzymes to form 4- oxo-alitretinoin. Both compounds undergo isomerization into tretinoin (or isotretinoin) and their 4-oxo metabolites. After oral administration of alitretinoin, 4-oxo-alitretinoin is the main observed active circulating metabolite with an AUC which accounts for >70% of the AUC of the parent drug. The isomers of alitretinoin (tretinoin, isotretinoin) and 4- oxo-alitretinoin (4-oxo-tretinoin and 4-oxo-isotretinoin) are minor accounting for ≤12% of exposure of parent drug. 4-oxo-alitretinoin is further glucuronidated and eliminated in urine.

There are no consistent time-dependent changes (neither induction nor accumulation) in the pharmacokinetics of alitretinoin or its measured metabolites.

Alitretinoin is an endogenous retinoid. Alitretinoin concentrations return to endogenous levels within 2 to 3 days after treatment cessation.

Elimination

Excretion of a radio-labeled dose of alitretinoin, was complete with approximately 94% of the dose recovered within 14 days. Radio-labeled material was eliminated mainly in urine as metabolites (63%, with <1% as unchanged parent drug) and with a smaller fraction (approx. 30% with 1% as unchanged parent drug) in feces. The most abundant excretion compound is the glucuronide of 4-oxo-alitretinoin amounting to 6.5% of the dose in urine.

The elimination half-life averaged 9 hours for alitretinoin and 10 hours for 4-oxo- alitretinoin.

Drug Interactions

Effect of alitretinoin on the pharmacokinetics of concomitant medications

A model based on *in vitro* data predicted that alitretinoin may increase the exposure of CYP2C8 substrates, with a 40% increase in the AUC of cerivastatin (a sensitive probe substrate), consistent with weak inhibition by alitretinoin (see **DRUG INTERACTIONS**).

Models based on *in vitro* data predicted that alitretinoin administration does not affect the exposure of concomitant medications that are substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, P-glycoprotein (P-gp), organic anion transporting polypeptide 1B1 (OATP1B1), organic anion-transporting polypeptide 1B3 (OATP1B3), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and organic cation transporter 2 (OCT2).

A clinical study showed that alitretinoin does not affect the exposure of concomitant medications that are CYP3A4 substrates (e.g. ketoconazole, ciclosporin A), including sensitive CYP3A4 substrates.

A clinical study showed decreases (by 13 to 24%) in simvastatin and simvastatin acid exposure in the presence of alitretinoin establishing that the potential for alitretinion to inhibit CYP3A4 and breast cancer resistance protein (BCRP) is low.

Effect of concomitant medications on the pharmacokinetics of alitretinoin

Co-administration of alitretinoin with a single dose of ketoconazole 200 mg (a potent CYP3A4 inhibitor, a weak CYP2C8 and CYP2C9 inhibitor, and a P-gp inhibitor) increased the C_{max} of alitretinoin by ~50% and 4-oxo-alitretinoin by ~13%; similar increases were seen with AUC (see **DRUG INTERACTIONS**).

A clinical study showed that co-administration of alitretinoin with simvastatin or ciclosporin A did not result in any clinically relevant changes in the pharmacokinetics of alitretinoin. Therefore co-administration of alitretinoin with medications that inhibit OATP, P-gp, and BCRP transporters are not expected to result in clinically relevant changes in the systemic exposure of alitretinoin.

Special Populations and Conditions Pharmacokinetics in special populations

The pharmacokinetics of alitretinoin and its measured metabolites in special populations (obesity, gender, age, and renal impairment) were evaluated in a study in 32 subjects with moderate to severe CHE receiving alitretinoin for 12 to 24 weeks. These analyses showed:

Obesity

Increased body weight or body mass index (BMI) does not result in clinically significant changes in alitretinoin or 4-oxo-alitretinoin exposure.

Gender

There are no clinically significant gender-related differences in alitretinoin or 4-oxo- alitretinoin AUC and C_{max}.

Elderly

While the pharmacokinetic data in elderly subjects is limited (n=6 over 60 years of age and n=3 over 65 years of age), there does not appear to be a relationship between increasing age and the dose-normalized AUC or C_{max} of alitretinoin or 4-oxo-alitretinoin.

A longitudinal dose-response model from clinical efficacy studies shows that elderly subjects (n=126) have an earlier and more pronounced response to treatment and are less likely to relapse, but are more likely to experience elevated triglyceride levels after 12 to 16 weeks of treatment.

STORAGE AND STABILITY

HANZEMA should be stored between 15° to 30°C. Store in the original carton to protect from light. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Store in the original package. Keep the blister strips in the outer carton to protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

10 mg soft gelatin capsule: Opaque, brown oval-shaped soft gelatin capsule imprinted with R6 in white ink.
Each capsule contains 10mg alitretinoin. The nonmedical ingredients are: DL-α-tocopherol, Gelatin, Glycerin, Medium chain triglycerides, Glyceryl distearate, Glyceryl Monooleate, Sorbitol, Soybean oil, Water, iron oxide red, iron oxide black.

30 mg soft gelatin capsule: Opaque, red-brown oval-shaped soft gelatin capsule imprinted with R7 in white ink.
Each capsule contains 30mg alitretinoin. The nonmedical ingredients are: DL-α-tocopherol, Gelatin, Glycerin, Medium chain triglycerides, Glyceryl distearate, Glyceryl Monooleate, Sorbitol, Soybean oil, Water, iron oxide red, iron oxide yellow.

The imprinting Opacode® S-1-7085 white contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

Availability: Boxes of 3 blister strips. Each strip contains 10 capsules.

PART II: SCIENTIFIC INFORMATION

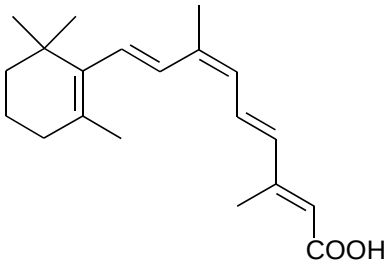
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Alitretinoin
Chemical name: (2*E*, 4*E*, 6*Z*, 8*E*)-3,7-Dimethyl-9-(2,6,6-tri-methyl-cyclohex-1-en-yl)-nona-2,4,6,8-tetraen-1-oic acid

Molecular formula and molecular mass: $C_{20}H_{28}O_2$ (300.44 g/mol).

Structural formula:



Physicochemical properties: Alitretinoin is a yellow to orange crystalline powder, with a melting point 190-191°C. Alitretinoin is only very slightly soluble in aqueous solutions. Alitretinoin is soluble (to different degrees) in various organic solvents. Alitretinoin has a pKa value of 4.73±0.33. Alitretinoin has a pH of 6.1 (1 % suspension in water).
The n-octanol/water partition coefficient (log P_{ow}) is 6.263±0.358

CLINICAL TRIALS

The safety and efficacy of alitretinoin in patients with severe chronic hand eczema (CHE) refractory to high potency topical corticosteroids has been evaluated in double blind, placebo-controlled Phase 3 studies. In these trials, the term Chronic Hand Dermatitis (CHaD) was used and is considered to be synonymous with Chronic Hand Eczema (CHE).

The primary endpoint in these studies was the proportion of patients achieving Physicians Global Assessment (PGA) ratings of clear or almost clear hands at the end of therapy. The treatment duration was 12 to 24 weeks.

The BACH (Benefit of Alitretinoin in Chronic Hand Dermatitis Study – BAP00089) included 1032 severe CHE patients who had no response or a transient response (initial improvement and worsening of disease despite continued treatment) to potent topical corticosteroids or were intolerant of potent topical corticosteroids. All phenotypes of CHE were included; approximately 30% of patients had hyperkeratotic only CHE, however the majority of patients had multiple phenotypes (i.e. hyperkeratosis (87%), pompholyx (27%), fingertip dermatitis

(43%), and other (15%)). Essentially all patients had signs of skin inflammation, comprising of erythema and/or vesicles. Treatment with alitretinoin led to a significantly higher proportion of patients with clear/almost clear hands, compared to placebo. The response was dose dependent (see Table 5).

Table 5 Primary Efficacy Parameter – Results

	Alitretinoin		
Primary Endpoint	**10 mg**	**30 mg**	**Placebo**
ITT Population	**N=418**	**N=409**	**N=205**
PGA at end of study			
Total Response Rate	115 (27.5%)	195 (47.7%)	34 (16.6%)
Clear	39 (9.3%)	90 (22.0%)	6 (2.9%)
Almost clear	76 (18.2%)	105 (25.7%)	28 (13.7%)
Comparison to placebo	P=0.004	P<0.001	

Secondary endpoints included: Time to response; Time to relapse for responding patients (i.e. duration of response); Proportion of patients with at least partial response based on PGA (PGA rating of clear, almost clear, or mild disease); Patient Global Assessment (PaGA); Change in modified total lesion symptom score (mTLSS) and Extent of disease (see Table 6).

Table 6 Secondary Efficacy Parameters – Results

	Alitretinoin		
Efficacy Variable **ITT Population**	**10 mg** **N=418**	**30 mg** **N=409**	**Placebo** **N=205**
Partial Response Rate (clear, almost clear or mild disease)	207 (49.5%)	254 (62.1%)	74 (36.1%)
PaGA (clear or almost clear)	101 (24.2%)	163 (39.9%)	31 (15.1%)
mTLSS (mean % change from baseline)	-50.79 (n=411)	-60.80 (n=408)	-37.30 (n=204)
mTLSS (median % change from baseline)	-56.25	-75.00	-38.68
Time to response (first quartile)	171 days (n=418)	85 days (n=409)	- (n=205)
Extent of disease (mean % change from baseline)	-40.01 (n=402)	-54.15 (n=391)	-31.93 (n=197)

Re-treatment Study (BAP00091)

The objective of the study was to assess the safety and efficacy of a 12 to 24-week course of alitretinoin in patients with chronic hand eczema refractory to topical therapy, who had been previously treated with alitretinoin or placebo in the BACH study. The numbers of responding patients without observed relapse at the end of the 24-weeks follow-up period was 62.6% (30 mg), and 70.4% (10 mg).

Responding patients from Study BAP00089 who relapsed within 24 weeks after the end of treatment were enrolled into Cohort A in a double-blind, randomized, placebo-controlled, multicenter study design. Relapse was defined as an mTLSS score ≥ 75% of the original baseline value (at baseline of Study BAP00089).

Eligible patients were assigned to the same dose they had previously received in Study BAP00089 or placebo in a 2:1 ratio for 12 to 24 weeks.

The efficacy results from this study suggest that patients who had previously responded to active alitretinoin can benefit from re-treatment (see Table 7).

Table 7 Summary of Primary Efficacy Variable - PGA (BAP00091 Cohort A)

Dose Group in BAP00089	**10 mg**		**30 mg**		**Placebo**
Dose group in BAP00091	**10 mg**	**Placebo**	**30 mg**	**Placebo**	**Placebo**
ITT Population	**N=21**	**N=10**	**N=49**	**N=24**	**N=13**
PGA at end of study					
Total Response Rate	10 (47.6%)	1 (10%)	39 (79.6%)	2 (8.3%)	9 (69.2%)
Clear	2 (9.5%)	1 (10%)	21 (42.9%)	0	3 (23.1%)
Almost clear	8 (38.1%)	0	18 (36.7%)	2 (8.3%)	6 (46.2%)

Patients in Cohort A who were treated with alitretinoin responded more frequently than those given placebo. In the alitretinoin 30 mg arm, 79.6% of patients responded (clear or almost clear in Physician's Global Assessment) compared with 8.3% on placebo. In the 10 mg arm 47.6% responded on active re-treatment compared to 10% on placebo. The placebo response rate in patients who previously responded to placebo was 69.2%. It thus appears that patients who responded to placebo treatment can respond again (intervention effect). Patients who had previously responded to active treatment, however, did not generally respond to placebo.

Non-responding patients with mostly mild or moderate CHE (following protocol amendment to exclude patients with severe disease) following 12 or 24 weeks of trial treatment in Study BAP00089 were enrolled into Cohort B in an open-label, multicenter study. All non-responding patients (Cohort B) were assigned to alitretinoin 30 mg once daily for 12 to 24 weeks.

Results for Cohort B indicate that either a higher dose or a longer treatment period can benefit patients who have residual mild or moderate CHE at the end of a course of 24 weeks of alitretinoin treatment. The overall response rate for the alitretinoin 30 mg group was 47.3% which is comparable to the response rate for the 30 mg arm in Study BAP00089.

ECG Safety

In a double-blind, placebo-controlled, crossover study in 48 healthy volunteers, alitretinoin was associated with statistically significant increases in the ECG-derived heart rate. In subjects receiving alitretinoin 30 mg for 3 days, the maximum mean increase was 4.4 bpm (90% CI 2.0,6.7 bpm) at 3 hours post-dosing. In subjects receiving a single dose of alitretinoin 60 mg, significant increases in heart rate were observed from 3 to 12 h post-dosing, with a maximum

mean increase of 10.6 bpm (90% CI 7.2,14.0 bpm) at 8 h post-dosing. The incidence of heart rate values greater than 100 bpm and =25% higher than baseline was 8.7% for the placebo treatment, 8.3% for the alitretinoin 30 mg treatment, and 23.9% for the alitretinoin 60 mg treatment.

Comparative Bioavailability Studies

A blinded, randomized, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study comparing a 1 x 10 mg single dose of Alitretinoin Soft Gelatin Capsules, 10 mg from Dr. Reddy's Laboratories Inc., USA with a 1 x 10 mg single dose of TOCTINO® (Alitretinoin) Soft Capsules, 10 mg from GlaxoSmithKline Inc., Canada., was conducted in healthy adult, male subjects under high-fat, high-calorie fed conditions. The results obtained from the 24 subjects who completed the study are summarized in the following table.

Table 8 Comparative Bioavailability Study for Alitretinoin, 10mg

Alitretinoin (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference$^{\Psi}$	% Ratios of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	161.4 169.3 (31.9)	164.7 169.3 (24.2)	98.0	91.1 - 105.4
$AUC_I$$^{\#}$ (ng.h/mL)	161.6 166.8 (28.7)	168.7 173.1 (23.4)	95.8	89.2 - 102.8
C_{max}(ng/mL)	61.4 69.4 (47.3)	60.3 66.1 (41.8)	101.8	85.9 - 120.7
T_{max}§ (h)	3.4 (48.7)	2.9 (46.3)		
$T_{½}$$^{\S\#}$ (1/h)	2.9 (23.0)	3.1 (27.2)		

* Alitretinoin Soft Gelatin Capsules, 10 mg of Dr. Reddy's Laboratories, Inc., USA
Ψ Toctino® (Alitretinoin Soft Capsules) 10 mg by GlaxoSmithKline Inc., Canada, purchased in Canada
§ Expressed as the arithmetic mean (CV%) only
# n=23

A blinded, randomized, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study comparing a 1 x 30 mg dose of Alitretinoin Soft Gelatin Capsules, 30 mg from Dr. Reddy's Laboratories Inc., USA with a 1 x 30 mg dose of TOCTINO® (Alitretinoin) Soft Capsules, 30 mg from GlaxoSmithKline Inc., Canada., was conducted in healthy adult, male subjects under high-fat, high-calorie fed conditions. The results obtained from the 22 subjects who completed the study are summarized in the following table.

Table 9 Comparative Bioavailability Study for Alitretinoin, 30mg

Alitretinoin (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference$^{\Psi}$	% Ratios of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	579.1 612.2 (33.1)	577.1 611.5 (32.2)	100.3	91.7 – 109.8
AUC_I (ng.h/mL)	589.3 623.0 (33.0)	588.6 622.4 (31.7)	100.1	91.7 – 109.3
C_{max} (ng/mL)	208.2 237.8 (50.5)	204.2 235.1 (47.5)	102.4	83.8 – 125.2
T_{max}§ (h)	3.7 (31.2)	3.8 (37.4)		
$T_{½}$§ (1/h)	2.8 (41.1)	3.2 (32.9)		

* Alitretinoin Soft Gelatin Capsules, 30 mg of Dr. Reddy's Laboratories, Inc., USA
Ψ TOCTINO® (Alitretinoin Soft Capsules) 30 mg by GlaxoSmithKline Inc., Canada, purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Retinoids include natural compounds such as retinol (vitamin A), as well as synthetic compounds, such as etretinate and acitretin, and have been proven to be useful agents in the treatment of a variety of dermatological diseases. Alitretinoin (9-*cis* retinoic acid, BAL4079) is a naturally occurring endogenous retinoid, structurally related to vitamin A. It is a highly lipophilic compound, and in humans is protein bound in plasma (99.1%). Alitretinoin, and to a lesser extent its 4-oxo-metabolite, are known to bind and activate both the retinoic acid (RA) receptors (RARs) α, β, and γ, and the retinoid X receptors (RXRs) α, β, and γ. However, the actual mechanisms and the significance of this receptor binding capacity remain to be established. Recent studies demonstrated that in contact dermatitis (allergic and chemical), alitretinoin plays an anti-inflammatory and immunomodulatory role, by down-regulation of the production of chemokines in cytokine-induced dermal cells and suppression of the expansion of cytokine-induced leucocytes and antigen presenting cells.

Safety Pharmacology

Alitretinoin administered orally (20, 200, or 2000 mg/kg) had no relevant effect on the CNS in mice after a single dose. Alitretinoin administered orally (10 or 30 mg/kg) to dogs had no effect on cardiovascular or respiratory function or locomotor activity after a single dose. Although ECG measurements in the 4 week oral dog study revealed sinoatrial block at the high dose of 30 mg/kg/day in 2 females only, no ECG effects were noted in the 26 week and 39 week studies.

The effect of alitretinoin on hERG tail current was studied at concentrations up to 30 μM, the solubility limit in this test system. The maximum inhibition at 30 μM was 26.42%, and an IC_{50} could not be determined.

TOXICOLOGY

Acute Toxicity Studies

The acute toxicity of alitretinoin was low in mice after intraperitoneal administration with an LD_{50} >4000 mg/kg at 24 hours after administration and approximately 1400 mg/kg after a 10-day observation period. The acute toxicity of alitretinoin was in line with the established low acute toxicity of retinoids in general and lower than that of all-trans and 13-cis retinoic acid.

Long-Term Toxicity Studies

In repeat dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 39 weeks), alitretinoin exhibited a toxicity profile characteristic of hypervitaminosis A, similar to other retinoids.

Retinoid toxicity was dose-dependent in all species investigated. The dose-limiting toxic effects of alitretinoin were bone fractures in rats, and skin and mucus membrane effects in dogs. Toxic effects were generally reversible following 4 weeks in the rat and up to 8 weeks in the dog.

In mice, the key findings included impaired general condition, minor changes in clinical chemistry parameters (increased triglycerides and alkaline phosphates, and decreased albumin/globulin ratio), degenerative changes of the testes, bone dystrophy, keratitis, and degenerative and inflammatory changes of the skin.

Test article-related effects were minimal in degree and were observed at doses ≥10 mg/kg/day. Therefore, the NOAEL in the 13 week mouse toxicity study was considered to be 3 mg/kg/day (gender mean C_{max}=59.6 ng/mL, AUC_{last}= 129.6 ng.h/mL).

In rats, retinoid-specific toxicity manifested as impaired general condition, minor changes of hematological and clinical chemistry parameters (reduced red blood cells and increased triglycerides), glycogen storage and fatty change of the liver, bone fractures, thickening of epiphyseal cartilage, hyperplasia and hyperkeratosis of the forestomach and esophagus, degenerative changes in the female reproductive organs and eyes, and medullary calcification of the kidneys.

Test article-related effects were observed generally at doses ≥2 mg/kg/day only. There were no findings of toxicological importance at a dose of 0.67 mg/kg/day. Therefore, the NOAEL in the 26 week rat toxicity study was considered to be 0.67 mg/kg/day.

In dogs, dermal symptoms (erythema, increased cerumen production, mild hair loss, and acanthosis), conjunctivitis, weight loss, minor changes of clinical chemistry parameters (increased triglycerides, reduced creatinine and total bilirubin, increased aspartate

aminotransferase (AST) and gamma glutamyl transpeptidase (GGT) activity, increased globulin, decreased albumin, and increased glutamate dehydrogenase (GLDH) activity), degenerative lesions of the kidneys, liver hypertrophy and changes in male and female reproductive organs were seen. As with other retinoids, reversible effects on male reproductive organs (disturbed spermatogenesis and associated degenerative lesions of the testes) were observed in dog studies ≥4 weeks duration at doses ≥6 mg/kg/day.

Systemic exposure (AUC_{last}) at the no-effect level of toxicity to male reproductive organs in the dog ranged from 2.0X to 3.8X the expected human exposure for a 30 mg dose. Test article-related effects were mostly minimal to slight in degree and were observed at doses ≥2 mg/kg/day. Therefore the NOAEL in the 39 week dog toxicity study was considered to be 0.7 mg/kg/day (gender mean C_{max}= 353.24 ng/mL, AUC_{last}= 640.4 ng.h/mL).

The table below depicts the principal toxicological findings in rats and dogs following oral administration of alitretinoin.

Table 10

Finding	Rat		Dog	
	Effect Dose (mg/kg/day)	No Effect Dose (mg/kg/day)	Effect Dose (mg/kg/day)	No Effect Dose (mg/kg/day)
Mortality/Morbidity				
Spontaneous bone fracture (females)	6	2	NO	NO
Body Weight Loss	NO	NO	2	0.7
Liver				
Increased liver weight	0.67 (males) 2 (females	NO (males) 0.67 (females)	NO	NO
Increased ALT	0.67	NO	NO	NO
Increased AST	0.67	NO	6	2
Increased γ-glutamyl transferase activity	NO	NO	6	2
Hepatocyte hypertrophy/granulation and periportal vacuolation	6	2	NO	NO
Thyroid follicular cell hypertrophy/hyperplasia	2	0.67	NO	NO
Bone				
Spontaneous bone fracture (females)	6	2	NO	NO
Increased periosteal mineralization in femur (males) and subperiosteal osteoclastic activity	2	0.67	NO	NO
Increased ALP	0.67	NO	NO	NO
Decreased plasma calcium concentration	0.67	NO	NO	NO
Decreased bone weight	6	2	NO	NO
Red Blood Cell				
Reduced hemoglobin, red blood cell count, packed and mean cell volume	6	2	6 (males)	2 (males)
Increased platelet count	2 (females) 0.67 (males)	0.67 (females) NO (males)	2 (males)	0.7 (males)
Increased total bilirubin	0.67	NO	NO	NO
Decreased creatinine and total bilirubin	NO	NO	6	2
Increased hemopoiesis in the liver and spleen (females)	6	2	NO	NO
Male Reproductive Organs				
Decreased testes and prostate gland weights	NO	NO	6	2
Increased tubular degeneration (partly with vacuolation) in testes	NO	NO	2	0.7
Tubular hypoplasia in testes	NO	NO	6	2
Decreased spermatids in epididymides	NO	NO	6	2
Prostate gland atrophy	NO	NO	6	2
Intestine				
Increased inflammatory cell infiltration	6 (females) 2 (males)	2 (females) 0.67 (males)	NO	NO
Skin/Mucous Membranes				
Erythema of the ears	NO	NO	0.7	NO
Kidney				
Calcium deposits medulla	10	3	NO	NO
Tubular nephrosis focal	NO	NO	10	3
Protein and Lipid Metabolism				
Increased triglycerides	2	0.67	6	2
Increased cholesterol (females)	0.67	NO	NO	NO
Decreased albumin and albumin:globulin ratio	0.67	NO	6	2

Key:

ALP = Alkaline phosphatase. ALT = Alanine aminotransferase. AST = Aspartate aminotransferase.

NO = Not observed.

Carcinogenicity

The carcinogenic potential of alitretinoin was assessed in mice and rats following oral administration for 104 weeks.

In the 104 week oral mouse carcinogenicity study, CD-1 mice were administered daily doses of alitretinoin at 3, 10, or 30 mg/kg/day. Clinical findings included deterioration of general condition and localized hair loss, and significantly impaired body weight development in males from approx. week 68 onwards. Dose-dependent non-neoplastic lesions were seen at 10 and 30 mg/kg/day (M>F) and included amyloidosis, degenerative changes of the testes and accessory sex glands, hepatocellular necrosis, myelopoietic hypercellularity of the bone marrow, increased incidence of chronic reactive hyperplasia of mandibular lymph nodes, bone atrophy and fibrous osteodystrophy, dystrophic and inflammatory changes of the cornea, and inflammatory and degenerative changes of the skin. Neoplastic lesions were limited to a borderline (male: 1 in 50; female: 3 in 50; historical background: 2%) increase in osteosarcoma at 10 mg/kg/day. Due to the absence of respective lesions in the high dose group (30 mg/kg/day), the osteosarcomas were considered as secondary to the dystrophic lesions of the bone in this dose group. As seen with other retinoids, the overall number of tumors was slightly reduced in mice treated at high doses. In summary, alitretinoin was found to be non-carcinogenic in mice at doses up to 30 mg/kg/day.

In the 104 week oral rat carcinogenicity study, Wistar rats were administered daily doses of alitretinoin at 0.5, 1, or 3 mg/kg/day by gavage in rapeseed oil. Clinical findings were limited to a minimally increased incidence of lenticular opacity in female rats at the high dose. Minor changes of hematological parameters (e.g. reduced red blood cell count, increased platelet count) were in line with findings noted in previous studies and are known effects of prolonged retinoid administration. At necropsy, enlarged livers at 1 and 3 mg/kg/day and accentuated lobular pattern and increased number of foci in the liver of female rats were seen at 3 mg/kg/day. Dose-dependent non-neoplastic lesions included increased glycogen storage, hypertrophy, and fatty change of the liver, hyperkeratosis and squamous cell hyperplasia of the esophagus and forestomach, ovarian atrophy, follicular hypertrophy of the thyroid gland (considered as secondary to liver cell hypertrophy and consequently enhanced liver enzyme activity), and focal endostosis in bone. Findings were minimal at daily doses of 0.5, slight at 1, and moderate at 3 mg/kg/day. Dose- dependent retinoid-specific toxicity was observed at 1 and 3 mg/kg/day in line with findings noted in previous toxicity studies. No neoplastic findings related to alitretinoin were seen in any group; therefore, alitretinoin was considered non-carcinogenic in rats at doses up to 3 mg/kg/day.

Reproduction and Teratology Studies

Due to the known teratogenic potential of retinoids, the reproductive and development toxicity studies conducted with alitretinoin were limited. Alitretinoin was found to be teratogenic in an *in vitro* Limb bud cell assay and in an exploratory embryotoxicity/teratogenicity study in mice. Alitretinoin had no influence on fertility and early embryonic development to implantation in rats, despite manifestation of retinoid-specific toxicity at the high dose (10 mg/kg/day) which reached similar plasma concentrations as those observed in humans. In addition, reversible effects on male reproductive organs, disturbed spermatogenesis, and associated degenerative lesions of the testes were observed at high doses in mice and dogs. Testicular toxicity is a known effect of retinoids in experimental animals and is considered to be related to alterations in endogenous retinoid homeostasis.

Mutagenicity Testing
Genotoxicity testing *in vitro* with the Ames test and human chromosome aberration assay (HCA), and *in vivo* with the micronucleus test (MNT), showed no genotoxic activity. The 5,6-epoxy-9-cis-retinoic acid (5,6-epoxide) impurity/degradant product did not exhibit mutagenic activity in the Ames II™ assay or clastogenic activity in the *in vitro* micronucleus test when spiked in alitretinoin at 0.5% . The 5,6-epoxide was negative for genotoxic potential in a combined mouse micronucleus and Comet study.

Photoxicity Testing
Alitretinoin absorbs light in the UV-A range. The phototoxic potential of alitretinoin was confirmed *in vitro* and *in vivo* after dermal application. Phototoxicty after oral administration was not examined.

Local Tolerance Testing
In a cumulative skin irritation study in rats marked skin irritation was observed with alitretinoin at all concentrations tested (0.5-1.3%).

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PART III: CONSUMER INFORMATION

PrHANZEMA
Alitretinoin capsules
10 mg and 30 mg

This leaflet is part III of a three-part "Product Monograph" published when HANZEMA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HANZEMA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
HANZEMA is used for adults with severe chronic hand eczema that has not improved after topical treatments, including steroids.

HANZEMA capsules are not to be given to children or adolescents less than 18 years old.

HANZEMA should be used under the care of a doctor who is knowledgeable in the use of systemic retinoids.

What it does:
The active substance in HANZEMA is alitretinoin. It belongs to a group of medicines known as retinoids which are related to vitamin A. Alitretinoin is believed to modify the immune system and have an anti-inflammatory effect on the eczematous lesions by reducing the production of some substances responsible for inflammation, thereby reducing and helping to clear eczema.

When it should not be used:
Do not use HANZEMA if you:

- are pregnant or if you can become pregnant and are not using two effective birth control measures
- are breast feeding
- have liver disease
- have severe kidney disease
- have high blood cholesterol or raised triglycerides
- have uncontrolled thyroid disease
- have very high levels of vitamin A in your body (*hypervitaminosis A*)
- are allergic (*hypersensitive*) to alitretinoin or to other retinoids (such as isotretinoin), soya, peanuts, or any of the other ingredients of HANZEMA (other nonmedicinal ingredients are listed below).
- are taking tetracycline (a type of *antibiotic*)
- have a hereditary problem of fructose intolerance, as this product contains sorbitol

If any of these apply to you, **go back to your doctor without taking HANZEMA.**

What the medicinal ingredient is:
alitretinoin

What the important nonmedicinal ingredients are:
DL-α-tocopherol, Gelatin, Glycerin, Medium chain triglycerides, Glyceryl distearate, Glyceryl Monooleate, Sorbitol, Soybean oil, Water, iron oxide red, iron oxide black (10 mg capsules only), iron oxide yellow (30 mg capsules only).

The imprinting Opacode® S-1-7085 white contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and smethicone.

What dosage forms it comes in:
Soft gelatin capsule, 10 mg (brown) and 30 mg (red-brown).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

All Women: Birth defects:
HANZEMA can cause birth defects (deformed babies). It can also cause miscarriage, premature birth, or death of the baby. Therefore, adequate birth control measures are essential when taking HANZEMA. See **"What are the important warnings for women taking HANZEMA?"**

Treatment with systemic retinoids, including alitretinoin, may cause increased pressure in the brain, with symptoms such as headache, nausea, vomiting and visual disturbances.

For other serious side effects of HANZEMA, see "SERIOUS SIDE EFFECTSAND WHAT TO DO ABOUT THEM" Table below.

What are the important warnings for women taking HANZEMA?

- **Do not take HANZEMA if you are pregnant**
- **If you become pregnant, stop taking HANZEMA and contact your doctor immediately**
- **HANZEMA can cause deformed babies. There is an extremely high risk that your baby will be deformed if you are pregnant while taking HANZEMA. This risk exists even if HANZEMA is taken for a short time. If you are a woman of childbearing potential, your physician should have discussed this risk with you, and explained how to avoid becoming pregnant while taking HANZEMA.**
- **You must avoid becoming pregnant while you are taking HANZEMA and for at least one month after you stop taking HANZEMA.**
- **You must discuss effective birth control with your doctor before beginning HANZEMA treatment, and you must use effective birth control:**
  - **For at least one month before you start HANZEMA;**
  - **While you are taking HANZEMA; and**
  - **For at least one month after you stop taking HANZEMA;**

  Bearing in mind that any method of birth control can fail.

- **You must use two effective and complementary methods of birth control at the same time, even if you have a history of infertility or are not sexually active.**
- **Microdosed progesterone preparations (minipills) are not a suitable method of contraception during HANZEMA therapy.**
- **Do not take HANZEMA until you are sure that you are not pregnant.**
- **You must have two negative pregnancy tests at least 3 weeks apart before you start HANZEMA. Take pregnancy tests at doctor's visits on a monthly basis while on the drug and take a pregnancy test at a doctor's visit one month after stopping treatment with HANZEMA. If your menstrual period is abnormal in length and intensity, tell your doctor.You must wait until the second or third day of your next normal menstrual period before you start HANZEMA.**
- **Your doctor can write a prescription for no more than 30 days of treatment. A new prescription is needed for more treatment. Each new prescription must be started within 11 days from the last negative pregnancy test.**
- **Stop taking HANZEMA and contact your doctor immediately if you do become pregnant while taking HANZEMA or during the first month after treatment has stopped, if you miss your period, or if you have sexual intercourse without using effective birth control. You should discuss with your doctor the serious risk of your baby having severe birth deformities because you are taking or have taken HANZEMA. You should also discuss the desirability of continuing with your pregnancy.**
- **Do not breastfeed while taking HANZEMA.**
- **Do not take the supplement St John's Wort (Hypericum perforatum) if you are taking an oral contraceptive. St. John's Wort (Hypericum perforatum) can interact with oral contraceptives and may decrease their effectiveness in preventing pregnancy.**

You should have been counseled using the manufacturer's Patient Information and Pregnancy Prevention Program which includes:

- Comprehensive information about the risks of this drug
- A checklist of criteria you had to meet before receiving this drug
- Detailed information on birth control options
- An acknowledgement form for you to review and sign

Advice for men taking HANZEMA

Very low amounts of alitretinoin are present in the semen of men taking HANZEMA, but too little to harm the unborn baby of your partner.

All patients should read the rest of this Consumer Information.

Do not take HANZEMA unless you completely understand its possible risks and are willing to follow all of the instructions in this Consumer Information.

BEFORE you use HANZEMA tell your doctor or pharmacist if:

- you have ever had any mental health problems, including depression, suicidal behaviour or psychosis, or if you take medicines for any of these conditions.
- you have high blood cholesterol or triglycerides or have a blood lipid (fats) disorder, risk of heart problems or are obese, you may need blood tests more often. If your blood cholesterol or triglycerides stay high, your doctor may lower your dose, or take you off HANZEMA.
- you have been suffering from thyroid disease. HANZEMA may lower your thyroid hormone levels. If your thyroid hormone level is low, your doctor may prescribe supplements.
- you plan vigorous physical activity during treatment with HANZEMA.
- you have any food or drug allergies.
- you are taking any vitamin preparations or health food supplements that contain Vitamin A.
- what brand of contraceptives you are taking. There are certain types of contraceptives that should not be taken while on HANZEMA.
- you are taking an antibiotic (particularly tetracyclines).
- you have liver disease, kidney disease or high lipid levels in your blood
- you have diabetes. HANZEMA may increase blood sugar levels. Your doctor may request periodic tests for blood sugar levels during treatment, particularly if you already have diabetes or are overweight.

While taking HANZEMA:

- **Do not donate blood** while you take HANZEMA and for one month after stopping HANZEMA. If someone who is pregnant gets your donated blood, her baby may be exposed to HANZEMA and may be born with birth defects.
- **Do not share HANZEMA with other people**. It can cause birth defects and other serious health problems.
- **Minimise your exposure to sunlight** and avoid exposure to sun lamps. Your skin may become more sensitive to sunlight. Before you go out in the sun, use a sun protection product with a high protection factor (SPF 15 or higher).
- **Cut down on intensive physical activity**: HANZEMA can cause muscle and joint pain.
- **If you develop dry eyes,** contact your doctor as soon as possible This can be helped by the application of a lubricating eye ointment or tear replacement drops. If you wear contact lenses and experience dry eyes you may need to wear glasses for the duration of HANZEMA treatment. Dry eyes and sight problems normally return to normal once treatment is stopped
- **If you experience any problems with your sight**, **tell your doctor immediately**. You should not drive or operate machinery. HANZEMA may need to be stopped and your sight monitored.
- **If you get a persistent headache,** nausea or vomiting (feeling or being sick) and blurred vision, these may be signs of a condition called benign intracranial hypertension. **Stop taking HANZEMA immediately** and contact your doctor as soon as possible.

- **If you have bloody diarrhea, severe diarrhea, abdominal pain or rectal bleeding, stop taking HANZEMA immediately** and contact your doctor as soon as possible.
- HANZEMA may change your liver enzyme levels, cholesterol or triglyceride levels, blood sugar levels or thyroid function. Your doctor will test these during treatment.
- If you have a rash, swelling of your face or mouth, difficulty breathing, or feel unwell, you may be allergic to the ingredients in HANZEMA. Contact your doctor immediately.
- If your mood changes, you feel sad, angry, or notice other emotional problems, contact your doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all the medicines you take or have taken recently, including non-prescription or herbal medicines.

Tell your doctor or pharmacist if:

- you are taking ketoconazole, fluconazole, or miconazole (medicines used to treat fungal infections). Your doctor may decide to adjust your dose of HANZEMA.
- you are taking gemfibrozil (a medicine which is used to lower cholesterol), diosmin (used to treat hemorrhoids) or oxandrolone (an anabolic steroid). Your doctor may decide to adjust your dose of HANZEMA
- you are taking St John's Wort (a herb extract used to treat depression), protease inhibitors (used to treat HIV or hepatitis C) or any medicines for epilepsy or seizures. These may reduce how well the contraceptive pill works.
- you are taking methotrexate, which can increase the risk of liver toxicity when taken with retinoids (such as HANZEMA).

Don't take HANZEMA with these medicines:

- vitamin A supplements or tetracyclines (a type of antibiotic). This increases the risk of side effects.
- other retinoid medicines, such as isotretinoin or tazarotene

HANZEMA is not recommended with amiodarone (a medicine that helps to regulate heart rate).

HANZEMA can also affect how some other medicines work. These include:

- paclitaxel (used to treat cancer),
- rosiglitazone or repaglinide (used to treat diabetes).

Tell your doctor if you are taking any of these.

What brand of oral contraceptives ("birth control pill") are you taking? There are certain types of contraceptives that should not be taken while on HANZEMA, such as the low-dose, progesterone only "mini-pill". These may not work while you are taking HANZEMA. Please talk to your doctor about what would be the most effective type of contraceptive while you are taking HANZEMA.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

- Read your prescription label carefully and be sure to take the exact amount of medicine prescribed by your doctor, usually either 10mg or 30mg once a day. Your doctor may change your prescribed dose from time to time, therefore, it is important that you check the label each time you fill your HANZEMA prescription. If you have any questions, call your doctor.
- Swallow each capsule whole and don't chew them.
- It is important to take HANZEMA with a main meal, preferably at the same time each day. Be sure to return to your doctor as scheduled. It is important for your doctor to see you regularly, (every month for women of child bearing potential), when you are taking HANZEMA. Discuss your progress and any concerns with your doctor.
- A course of treatment usually lasts for 12 to 24 weeks depending on your disease. If your first treatment was successful, your doctor may prescribe another course of treatment if symptoms return.

Overdose:
In cases of overdose or suspected overdose, contact a healthcare practitioner (or doctor), hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you are a woman and have taken an overdose of HANZEMA, ask your doctor to test if you are pregnant. If *you* find out you are pregnant, stop taking HANZEMA and contact your doctor immediately.

Missed Dose:
If you forget to take a dose of HANZEMA it may be taken later the same day, but do not take more HANZEMA in one day than your doctor has prescribed. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, HANZEMA can cause side effects, although not everybody gets them.

- **Headache**
- **Raised blood fats**: higher levels of fats (triglycerides) and cholesterol in the blood
- **Blood cell disorders**: increase in the number of blood platelets (cells that help blood to clot), decrease in the number of red and white blood cells seen in blood tests
- **Thyroid problems**: decreased levels of thyroid hormones
- **Eye problems**: inflammation of the eye and eyelid area (conjunctivitis); eyes feel dry and irritated. **Ask a pharmacist for suitable eye drops.** If you wear contact lenses and get dry eyes, you may need to wear glasses instead.
- **Blood and circulation:** flushing, high blood pressure, inflammation of blood vessels, swelling of the hands, lower legs and feet
- **Muscle and joint pain:** back pain, muscle pain, joint

pain. High levels of muscle breakdown products in your blood if you exercise vigorously.
- **Skin, nail and hair problems:** dryness of the skin, especially of the lips and face, inflamed skin, redness of the skin, itchy skin, skin peeling, rash, dry skin eczema, itchy skin rash, hair loss, increased sensitivity of the skin to sunlight, nail disorders
- **Liver problems:** raised liver enzymes seen in blood tests
- **Sensory problems**: dizziness, persistent noise in the ears
- **General**: nausea, vomiting, dry mouth, lack of energy (fatigue)
- **Ear, nose and throat problems:** nose bleeding
- **Bone disorders**: extra growth of bone, including the spine disorder ankylosing spondylitis
- **Stomach problems:** indigestion
- **Vision:** blurred, distorted vision, difficulty seeing at night. If you suffer these problems, do not drive or operate machinery until these symptoms have passed. If vision problems persist, contact your doctor and your doctor may stop HANZEMA treatment and may refer you to an eye specialist.

Side effects of other medicines in the same family of medications as HANZEMA.
The following effects haven't yet been seen in HANZEMA but have occurred in this product class and may occur.

- **Diabetes**
  Excessive thirst; frequent need to urinate; blood tests show an increase in your blood sugar.
- **Bone disorders**
  Arthritis; bone disorders (delayed growth, changes to bone density); growing bones may stop growing.
- **Visual disorders**
  Colour blindness and colour vision gets worse.

		or pharmacist right away	call your doctor or pharmacist right away
Common	**Depression and other mental problems** including sad or empty mood, mood changes, tearfulness, and emotional disorder. Some people have had thoughts about harming themselves or ending their lives, have attempted suicide or committed suicide. These people may not appear to be depressed. Your doctor can arrange help. You should tell a family member or close friend that you can become depressed, or have significant changes in mood or behaviour, and ask them to read this leaflet. You might ask them to look after you.	✓	
Uncommon	**Sight problems** including blurred vision, distorted vision, cloudy surface on the eye (corneal opacity, cataracts).		✓
Rare	**Severe allergic reaction** including swelling of the face or mouth causing difficulty in breathing (angioedema), raised and itchy rash (hives).		✓
	Immune reaction including vasculitis (swelling of the blood vessel) with symptom such as bruises and red patches.		✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor**	**Stop taking drug and**

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Symptom / effect	**Talk with your doctor or pharmacist**	**Stop taking drug and call your**

		right away	doctor or pharmacist right away
Rare	**Benign Intracranial Hypertension** Lasting headache along with feeling sick (nausea), being sick (vomiting), and changes in your eyesight including blurred vision.		✓
Very rare	**Stomach disorders** Severe abdominal (tummy) pain, with or without bloody diarrhea, feeling sick (nausea) and being sick (vomiting). These can be signs of serious abdominal conditions.		✓
Unknown	**Keratitis** (inflamed cornea).		✓
	Pancreatitis (inflammation of the pancreas) which can be fatal, with symptoms such as abdominal pain, nausea, vomiting, diarrhea and fatty stool.		✓

This is not a complete list of side effects. For any unexpected effects while taking* HANZEMA, *contact your doctor or pharmacist.

HOW TO STORE IT

- **Keep out of the sight and reach of children**
- HANZEMA should be stored between 15° to 30°C. Store in the original carton to protect from light. Do not freeze.
- Return any unused capsules to your pharmacist at the end of treatment

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about HANZEMA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Dr. Reddy's Laboratories Canada Inc. web site www.drreddys.com or by calling Dr. Reddy's Laboratories Canada Inc. at 1-855-845-1739.

To report an adverse event related to HANZEMA, please contact 1-855-845-1739.

This leaflet was prepared by Dr. Reddy's Laboratories, Inc.

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