Europe
Teva Pharmaceuticals Europe B.V.

EU RISK MANAGEMENT PLAN

Capsaicin

RMP version to be assessed as part of this application	
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Local Safety Officer Details

Local Safety Officer name: [redacted]

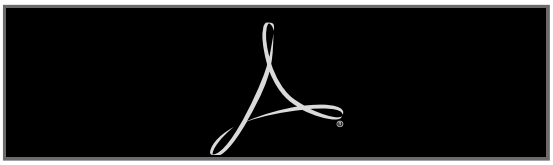
Local Safety Officer signature: 

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	Not applicable for initial version.	Not applicable.
Part II - Module SI Epidemiology of the indication(s) and target population(s)	Not applicable.	Not applicable.
Part II - Module SII Non-clinical part of the safety specification	Not applicable.	Not applicable.
Part II - Module SIII Clinical trial exposure	Not applicable.	Not applicable.
Part II - Module SIV Populations not studied in clinical trials	Not applicable.	Not applicable.
Part II - Module SV Post-authorisation experience	Not applicable.	Not applicable.
Part II - Module SVI Additional EU requirements for the safety specification	Not applicable.	Not applicable.
Part II - Module SVII Identified and potential risks	Not applicable.	Not applicable.
Part II - Module SVIII Summary of the safety concerns	Not applicable.	Not applicable.
Part III Pharmacovigilance plan (including post-authorisation safety studies)	Not applicable.	Not applicable.
Part IV Plans for post-authorisation efficacy studies	Not applicable.	Not applicable.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Not applicable.	Not applicable.
Part VI Summary of the risk management plan	Not applicable.	Not applicable.
Part VII Annexes	Not applicable.	Not applicable.

Other RMP versions under evaluation	
RMP Version number	Not applicable.
Submitted on	Not applicable.
Procedure number	Not applicable.

Details of the currently approved RMP	
Version number	Not applicable for initial version.
Approved with procedure	Not applicable.
Date of approval (opinion date)	Not applicable.

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting-Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CTD	Common Technical Document
e.g.	example given
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HLT	High Level Term
i.e.	Id est (engl.: that means)
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
LSO	Local Safety Officer
MedDRA	Medical Dictionary for Regulatory Activities
MNT	Medical Nutrition Therapy
OA	Osteoarthritis
Ph. Eur.	European Pharmacopoeia
PHN	Postherpetic Neuralgia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SP	Safety Population (In Clinical Trials)
SmPC	Summary Of Product Characteristics
UK	United Kingdom
UKPDS	The United Kingdom Prospective Diabetes Study
US(A)	United States (of America)
WADA	World Anti-Doping Agency
WHO	World Health Organisation

Part I: Product(s) Overview

Table 2: Product(s) Overview

Active substance(s) (INN or common name)	**Capsaicin**
Pharmacotherapeutic group(s) (ATC Code)	Topical products for joint and muscular pain; Capsaicin and similar agents (M02AB01)
Marketing Authorisation Holder	Teva B.V.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Zacin (capsaicin) 0.025% w/w cream Axsain cream (capsaicin) 0.075% w/w cream
Marketing authorisation procedure	National
Brief description of the product	**Chemical class**: Capsaicin is an alkaloid that is active principle of the dried ripe fruits of *Capsicum* spp.
	Summary of mode of action: Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin exerts an analgesic effect by depleting and preventing re-accumulation of Substance P in peripheral sensory neurons. Substance P is considered the principal chemo mediator of pain impulses from the periphery to the central nervous system.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current**: **Zacin** (capsaicin) 0.025% w/w cream: For the symptomatic relief of pain associated with osteoarthritis. **Axsain** (capsaicin) 0.075% w/w cream: For the symptomatic relief of neuralgia associated with and following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed.

	For the symptomatic management of painful diabetic peripheral polyneuropathy.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	**Current**: **Zacin** (capsaicin) 0.025% w/w cream: For topical administration to unbroken skin. Apply only a small amount of cream (pea-size) to the affected area 3 or 4 times daily. The cream should be gently rubbed in and there should be no residue left on the surface. Hands should be washed immediately after application of capsaicin unless hands and fingers are being treated. Capsaicin should not be applied near the eyes. Pain relief usually begins within the first week of treatment and increases with continuing regular application for the next two to eight weeks. **Axsain** (capsaicin) 0.075% w/w cream: For topical administration to unbroken skin. Apply only a small amount of cream (pea-size) to the affected area 3 or 4 times daily. The cream should be gently rubbed in and there should be no residue left on the surface. Hands should be washed immediately after application of capsaicin with the fingers. Do not apply near the eyes. Patients using capsaicin for the treatment of painful diabetic peripheral polyneuropathy should only do so under the direct supervision of a hospital consultant who has access to specialist resources. The recommended duration of use in the first instance is 8 weeks, since there is no clinical trial evidence of efficacy for treatment of more than 8 weeks duration. After this time, it is recommended that the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter, by the supervising consultant.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: Zacin (capsaicin) 0.025% w/w cream Axsain (capsaicin) 0.075% w/w cream
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication

For **Zacin** (capsaicin) 0.025% w/w cream:

For the symptomatic relief of pain associated with osteoarthritis.

For **Axsain** (capsaicin) 0.075% w/w cream:

For the symptomatic relief of neuralgia associated with and following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed.

For the symptomatic management of painful diabetic peripheral polyneuropathy.

Incidence and prevalence:

Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder in the world and in Western populations it is one of the most frequent causes of pain, loss of function and disability in adults (Ardenand and Nevitt, 2006). The exact incidence and prevalence of osteoarthritis is difficult to determine because the clinical syndrome of osteoarthritis (joint pain and stiffness) does not always correspond with the structural changes of osteoarthritis (usually defined as abnormal changes in the appearance of joints on radiographs). This area is becoming more complex with sensitive imaging techniques such as magnetic resonance imaging, which demonstrate more frequent structural abnormalities than detected by radiographs. Osteoarthritis at individual joint sites (notably knee, hip and hand) demonstrates consistent age-related increases in prevalence. However, symptomatic osteoarthritis is an inevitable consequence of ageing. Although prevalence of osteoarthritis rises in frequency with age, it does affect substantial numbers of people of working age. The number of people with osteoarthritis in the UK is increasing as the population ages, and as the prevalence of risk factors such as obesity and poor levels of physical fitness also continues to rise (NCC-CC: Osteoarthritis, 2008). Farming 1-9 years increases the risk of osteoarthritis 4.5 times; farming 10 or more years increases the risk 9.3 times (Tanna, 2004).

Neuralgia associated with and following herper zoster

Postherpetic neuralgia (PHN) is a painful and often debilitating complication of acute herpes zoster virus infection that is characterized by intense neuropathic pain. The disorder, thought to occur due to inflammatory nerve injury during infection, may last months to years and causes intractable pain and morbidity (Lapolla et al. 2011).

United States: Frequency 1 month after onset of shingles is 9-14.3% and at 3 months is about 5%. At 1 year, 3% continue to have severe pain. Family history as a risk factor for herpes zoster has been described. In a case-control study of 504 patients and 523 controls, it was found that the patients were more likely to report blood relatives with herpes zoster than the controls (39% vs

11%, p< 0.001). This risk was higher in patients with multiple blood relatives with herpes zoster compared with those with a single blood relative with herpes zoster (McElveen and Gonzalez, 2012).

International: A study from Iceland demonstrated variations in risk of PHN associated with different age groups. No patient younger than 50 years described severe pain at any time. Patients older than 60 years described severe pain: 6% at 1 month and 4% at 3 months from the onset of shingles. (McElveen and Gonzalez, 2012).

Diabetic peripheral neuropathy

In the developed world, the most common cause of peripheral neuropathy is diabetes mellitus (England and Asbury, 2004).

Overall, 20–40% of people with diabetes are estimated to have neuropathy (depending on how it is defined and measured) and about 5% have a foot ulcer (McIntosh et al, 2003).

For the year 2013, 382 million people worldwide, or 8.3% of adults, were estimated to have diabetes. About 80% live in low- and middle-income countries. If these trends continue, by 2035 some 592 million people, or one adult in 10, will have diabetes. Global prevalence for diabetes (20-79 years) is estimated to be 8.3 %. The number of people with diabetes in Europe is estimated to be 56.3 million – 8.5% of the adult population. Turkey has the highest prevalence (14.8%) and the Russian Federation has the greatest number of people with diabetes (10.9 million) (IDF Diabetes Atlas, 2013).

Demographics of the population in the authorised indication and risk factors for the disease:

Osteoarthritis

There have been some attempts to estimate the number of people who might have significant clinical problems arising from osteoarthritic joint pathology. These have not been validated, but they suggest that about 10% of persons over the age of 60 are affected. Surveys have largely been conducted in the most developed countries but there is indirect evidence suggesting that this is a worldwide problem. The Scientific Group estimates that 10% of the world's population who are 60 years or older have significant clinical problems that can be attributed to osteoarthritis (WHO, 2003).

Radiographic evidence of OA occurs in the majority of people by 65 years of age and in about 80% of those aged over 75 years. In the US it is second only to ischaemic heart disease as a cause of work disability in men over 50 years of age, and accounts for more hospitalizations than rheumatoid arthritis (RA) each year (Ardenand and Nevitt, 2006). Worldwide estimates indicate that 9.6% of men and 18% of women ≥ 60 years have symptomatic OA (Tanna, 2004).

Country impact according to Tanna (2004):

Aggregate numbers on the overall impact of OA are not available. Therefore, statistical highlights and the impact of arthritis from individual countries that have reported information are presented.

UK

- In England and Wales between 1.3 and 1.75 million people have symptomatic OA. In 2000 more than 80,000 hip or knee replacements were performed at a cost of £405 million.
- As a cause of disability (such as walking and climbing stairs) in the elderly OA is second to cardiovascular disease.
- Altogether 10% to 15% of adults over 60 have some degree of OA.

Germany

- Four million people out of 82 million people suffer from some form of autoimmune conditions affecting joints.
- Most people participate in a universal medical health insurance system.
- The key issues in the fight against arthritis include access to medications, access to speciality care, uncoordinated treatment, and diminished state budgets.

Canada

- The direct and indirect costs of arthritis in Canada equates to approximately $18 billion per year.
- Over four million Canadians out of 31,014,000 people have arthritis.
- There are approximately 37,000 hip and knee replacement surgeries every year in Canada.
- The key issues in the fight against arthritis facing Canada include: access to medications, access to rheumatology care, access to orthopaedic care, funding for research and illness disability.

Japan

- Population of 127 million people.
- 17% of population is over 65 (this percentage is expected to grow by 25% in the next three decades).
- 5% of the population has some form of arthritis.
- The key issues in the fight against arthritis facing Japan include access to medications, access to speciality care.

US

- It is estimated that over 41 million people out of 285 million people in the United States have arthritis.
- In the United States about 6 percent of adults over 30 have OA of the knee and about 3 percent have OA of the hip.
- The occurrence of the OA increases with age, rising 2- to 10-fold in people from 30 to 65 years of age.
- An estimated 50 million people will be diagnosed with arthritis by 2013.
- The current economic burden of arthritis in its various forms is approximately $82.4 billion.
- Direct costs are $34.6 billion (hospitals, doctors, transportation, nursing homes)
- Only 3% of the cost is for drugs.
- Indirect costs are $47.8 billion (primarily lost wages and lost productivity).
- Arthritis is a greater factor in limiting activity than heart disease, hypertension, blindness, or diabetes. Figure 3 shows the levels of physical activity reported by women with arthritis in

the US. Only 24% of people with arthritis report and achieve levels of physical activity that are recommended for health. The remainder are essentially inactive or insufficiently active.

Osteoarthritis is defined not as a disease or a single condition but as a common complex disorder with multiple risk factors. These risk factors are broadly divisible into (NCC-CC: Osteoarthritis, 2008):

- genetic factors (heritability estimates for hand, knee and hip osteoarthritis are high at 40–60%, though the responsible genes are largely unknown)
- constitutional factors (for example, ageing, female sex, obesity, high bone density)
- more local, largely biomechanical risk factors (for example, joint injury, occupational/ recreational usage, reduced muscle strength, joint laxity, joint malalignment).

Neuralgia associated with and following herper zoster

No predilection for developing PHN is known. Although 65% of patients in a study by Watson et al were women, this was believed to mirror the usual predominance of women in this age group. The association between greater age and PHN is strong. At age 60 years, approximately 60% of patients with shingles develop PHN, and at age 70 years, 75% develop PHN (McElveen and Gonzalez, 2012).

Risk factors for developing PHN include older age (> 50 years), worse pain associated with the acute viral infection, extensive cutaneous involvement (eg, widespread blistering), and severe prodromal pain (Lapolla et al. 2011).

Univariate and multivariate analyses indicated that older age, female sex, presence of a prodrome, greater rash severity, and greater acute pain severity made independent contributions to identifying which patients developed PHN. Patients with subacute herpetic neuralgia who did not develop PHN were significantly younger and had less severe acute pain than PHN patients, but were significantly more likely to have severe and widespread rash than patients without persisting pain (Jung at al., 2004).

Diabetic peripheral neuropathy

In a survey of 2633 Spanish patients with diabetes, aged 15-74 years, 22.7% had diabetic polyneuropathy, diagnosed as a neuropathy Disability Score of >5 regardless of Neuropathy Symptom Score, or a Neuropathy Disability Score of 3-5 in conjunction with a Neuropathy Symptom Score of at least 5. No differences in prevalence were seen by sex, but the prevalence in insulin-dependent patients was 12.9% and in non-insulin dependent patients 24.1% ($p<0.001$). Prevalence increased with increasing age and with increasing duration of diabetes since diagnosis ($p<0.001$). Prevalence was lower in those attending primary care centres (21.0%) compared with those being treated in hospital clinics (26.7%) ($p<0.05$). Multiple logistic regression analysis found that age and duration of diabetes were both associated with diabetic polyneuropathy in Type 2 patients ($p<0.001$) whereas the association was only seen for duration of diabetes in Type 1 patients ($p<0.05$). A second model also found an association between the origin of patients (in terms of whether they attended, and were recruited from, hospital clinics or primary health care centres) as well as the other two factors, in Type 2 patients, with those from hospitals having higher prevalence ($p<0.001$) (McIntosh et al, 2003).

The primary risk factor for diabetic neuropathy is hyperglycaemia. The United Kingdom Prospective Diabetes Study (UKPDS) failed to support a similar correlation between the incidence of neuropathy and glycaemic control in type 2 diabetes patients, but the progression of diabetic neuropathy is dependent on glycaemic control in both type 1 and 2 diabetes patients, and the pathologies are considered similar. The duration of diabetes also increases the risk of neuropathy, but the association between duration and prevalence may depend in part upon patient age, which itself is a risk factor. Cigarette smoking, alcohol consumption, hypertension, height, and hypercholesterolemia are all considered independent risk factors for diabetic neuropathy (Duby et al. 2004).

The main existing treatment options:

Osteoarthritis

Persons with OA are a heterogeneous population, ranging widely in age, disease impairment, functional goals, and interests. Therefore management of the patient with OA should be comprehensive and individualized, taking into account the anatomical distribution, the phase and the progression rate of the disease. The management of OA is broadly divided into non-pharmacological, pharmacological, and surgical treatments. Surgical treatment is generally reserved for failed medical management with functional disability affecting a patient's quality of life (Tanna, 2004).

Exercise should be a core treatment for people with osteoarthritis, irrespective of age, comorbidity, pain severity and disability (NCC-CC: Osteoarthritis, 2008).

Neuralgia associated with and following herper zoster

Treatment of postherpetic neuralgia (PHN) is usually difficult and the pain may be unresponsive to treatment in 50% of cases (Dubinsky et al, 2004). Generally, tricyclic antidepressants, antiepileptics, and topical lidocaine are recommended as first-line analgesics for PHN, opioids and tramadol as second-line, and topical capsaicin and valproate as third-line analgesics. Combination therapy with more than 1 drug class may be beneficial in some patients (Wu and Raja, 2008).

Acyclovir and its analogues (ie, valacyclovir, famciclovir) speed the resolution of herpetic skin lesions and acute pain while reducing viral shedding. Tricyclic antidepressants and the anticonvulsant drug gabapentin may reduce the pain of PHN (Lapolla et al. 2011).

Drugs used in the treatment of acute herpes zoster include antivirals, analgesics, and systemic corticosteroids (Schmader and Dworkin, 2008).

Diabetic peripheral neuropathy

Symptomatic management is important for all types of neuropathy, including general preventive and palliative therapy as well as the treatment of specific problems such as neuropathic pain. Treatment of pain is an important aspect for many patients with chronic polyneuropathies. Neuropathic pain can be difficult to treat. Medications that are most useful include antiepileptic drugs, antidepressants, and tramadol. Some patients need opioid medications for adequate pain relief (England and Asbury, 2004). Common topical treatments for diabetic peripheral neuropathic pain include capsaicin cream and lidocaine 5% patches (Lindsay et al, 2010).

Meticulous foot care is essential for patients with diabetes and distal peripheral neuropathy. A multidisciplinary approach is recommended for diabetics with foot ulcers and other risks for feet complications, especially those with a history of prior ulcer or amputation (American Diabetes Association, 2008).

Glycaemic control, medical nutrition therapy (MNT), diabetes self-management education, physical activity, and psychosocial assessment and care are essential elements of the diabetes management plan (American Diabetes Association, 2013). Drug therapy includes: insulins, biguanides, sulfonylureas, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, antidiabetics (glucagon-like peptide 1 agonists, dipeptidyl peptidase-4 enzyme inhibitor, amylin mimetic agent), platelet aggregation inhibitors, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-adrenergic blockers and antihyperlipidemics.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Osteoarthritis

OA is the highest-ranking disease among the musculoskeletal diseases and a major cause of impaired mobility. In 1990, OA was estimated to be the eighth leading non-fatal burden of disease, accounting for 2.8% of total years of living with disability. 80% of those with osteoarthritis will have limitations in movement, and 25% cannot perform their major daily activities of life. Overall disease burden ranking according to this compiled data shows a ranking of 12 for combined 25 EU countries; 15th ranked for old EU and 9th rank for the 10 EU accession countries (Tanna, 2004).

Neuralgia associated with and following herper zoster

Postherpetic neuralgia is not fatal but patients may experience significant pain for a prolonged period of time and appears to be more frequent at older age (McElveen and Gonzalez, 2012).

Diabetic peripheral neuropathy

Loss of feeling is particularly dangerous because it can allow injuries to go unnoticed, leading to serious infections and ulceration, diabetic foot disease, and major amputations (IDF Diabetes Atlas, 2013).

In a large retrospective cohort study of 8,905 patients with Type 1 or Type 2 diabetes, in a health maintenance organisation (USA), the cumulative incidence for foot ulcers over three years (1993-1995) was 5.8%. Of these, 77 (15%) developed osteomyelitis and 80 (15.6%) required amputation. Survival at three years was lower for foot ulcer patients than for age and sex matched patients with diabetes but without foot ulcers (McIntosh et al, 2003).

Important co-morbidities:

Osteoarthritis predominantly affects older people, and often coexists with other conditions associated with aging and obesity, such as cardiovascular disease and diabetes, as well as with common sensory (for example, poor vision) and psychosocial problems (for example, anxiety, depression and social isolation) (NCC-CC: Osteoarthritis, 2008).

People with Type 2 diabetes are at high cardiovascular (CV) risk, high risk of diabetes eye damage, and high risk of renal disease (NCC-CC: Type 2 diabetes, 2008).

Part II: Module SII - Non-Clinical Part of the Safety Specification

No non-clinical studies have been performed by the MAH. The available animal toxicity relating to capsicum, capsicum extracts and capsaicin do not suggest that, in usual doses, they pose any significant toxicity hazard to man. Thus, in both single and repeat dosing studies which have been reported, capsicum extracts and capsicum are generally well-tolerated at many times even the highest estimated human intakes. The safety of capsaicin for use in human pregnancy has not been established since no formal reproduction studies has been performed in either animals or man. However, there is no reason to suspect from human or animal studies currently available that any adverse effects in humans are likely.

Studies reported in the published literature which relate to potential genotoxic and carcinogenic action of capsaicin have produced inconclusive and conflicting data. However, it is unlikely that capsaicin, in the quantities absorbed transdermally from capsaicin cream, will pose any significant hazard to humans.

Part II: Module SIII - Clinical Trial Exposure

SIII.1 Brief overview of development

Five double-blind, vehicle-controlled studies have been carried out as a phase IV studies in the USA in the period from 1988-1992. The objective of the first 4 studies was to evaluate the safety and efficacy of topically-applied capsaicin cream vs vehicle for the relief of pain associated with osteoarthritis or rheumatoid arthritis. The fifth double-blind study (015-01) was a clinical pharmacological investigation.

Study No.	Dose capsaicin	Diagnosis of patients[1]	Objectives
066-04	0.025%	OA	Safety and efficacy: as monotherapy in patients with primary or post-traumatic OA
109-01	0.025%	OA	Safety and efficacy: in patients with active primary OA of the hands
87-04	0.025%	OA&RA	Safety and efficacy: in patients with RA or OA of the knee joints
89-12	0.075%	OA&RA	Safety and efficacy: in patients with RA or OA of the hands
015-01	0.075%	RA	Clinical pharmacology: evaluating the effects of topical capsaicin cream applied qid for 4 weeks to the knees of patients with RA

[1]OA: osteoarthritis; RA: rheumatoid arthritis; M: male; F: Female

SIII.2 Clinical Trial exposure

Study Medication and Dosage Regimen	Study 066-04	Study 109-01	Study 87-04	Study 89-12	Study 015-01
	0.025% capsaicin qid vs placebo	0.025% capsaicin: qid-3 weeks, bid-6 weeks vs placebo	0.025% capsaicin qid vs placebo	0.075% capsaicin bid vs placebo	0.075% capsaicin qid vs placebo
Number of patients taking part in trial1	Total OA- 113 Capsaicin: 57 (23M/34F) Vehicle: 56 (18M/68F)	Total OA-59 Capsaicin: 29 (8M/21F) Vehicle: 30 (11M/19F)	Total OA-70 Total RA-31 OA Capsaicin: 36 (15M/21F) OA Vehicle: 34 (10M/24F)	OA-14 RA-7 OA Capsaicin:7 OA Vehicle: 7	RA: 10 (5 in each group)

Part II: Module SIV - Populations Not Studied in Clinical Trials

Only phase IV studies have been conducted in the late 1980ies and early 1990ies. That time was before the guidelines of the ICH series were issued (mid 1990ies) and far before the EU "Note for guidance on clinical investigations of medicinal products for treatment of nociceptive pain" (CPMP/EWP/612/00, issued 21 November 2002). For an existing product, however, also the long-lasting market experience should be considered.

Capsaicin creams are not suitable for use in children. Demographics of target populations indicate that all three conditions for which capsaicin is indicated are in first place disorders of adult and elderly population.

The safety of Axsain/Zacin during pregnancy or lactation has not been established in either humans or animals. However, in the small amounts absorbed transdermally from Axsain/Zacin Cream, it is considered unlikely that capsaicin will cause any adverse effects in humans.

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

An estimate of patient treated was obtained from sales data [2] by assuming a consumption of one package per patient.

Cumulatively (until 31 January 2014) approximately 1,825,751 patients were exposed to Teva Group products containing capsaicin.

[2] Sales data from Teva and acquired companies have been available since the following dates: Teva -2002; Pliva-January 2006; ratiopharm - November 2006; Cephalon - November 2008; Mepha - January 2009

SV.1.2 Exposure

By indication/dose		
Indication	**Dose**	**Exposure (packs/person)**
Symptomatic relief of pain associated with osteoarthritis	0.025% w/w cream	1,322,010
Symptomatic relief of neuralgia associated with and following Herpes Zoster infections (post-herpetic neuralgia) and Symptomatic management of painful diabetic peripheral polyneuropathy	0.075% w/w cream	503,741

By country		
EU	**Dose**	**Exposure (packs/person)**
Ireland	0.025% w/w cream	67,786
United Kingdom	0.025% w/w cream	1,232,313
Non-EU	**Dose**	**Exposure (packs/person)**
Argentina	0.025% w/w cream	7,023
Puerto Rico	0.025% w/w cream	76
United States	0.025% w/w cream	14,812
EU	**Dose**	**Exposure (packs/person)**
Ireland	0.075% w/w cream	24,326
United Kingdom	0.075% w/w cream	446,726
Non-EU	**Dose**	**Exposure (packs/person)**
Argentina	0.075% w/w cream	10,010
Puerto Rico	0.075% w/w cream	48
United States	0.075% w/w cream	18,936
Uruguay	0.075% w/w cream	3,695

SV.1.2 Post-authorisation use in populations not studied in clinical trials

There is no data on post-authorisation use in the special populations (patients with organ impairment).The product is not indicated for use in paediatric patients.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Capsaicin is not listed on World Anti-Doping Agency (WADA) list of Prohibited Substances (WADA prohibited list, 2014). No misuse for illegal purpose in human use is known for capsaicin. There is no potential for use as a recreational drug or facilitating assault etc.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

There are no safety concerns recognised for capsaicin.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Skin irritation
- Transient burning on application
- Irritation of the mucous membranes of the eyes and respiratory tract (such as nasal and throat irritation) on application of cream
- Coughing
- Sneezing
- Runny eyes
- Dyspnoea
- Wheezing
- Exacerbation of asthma

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no safety concerns recognised for capsaicin.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no safety concerns recognised for capsaicin.

Part II: Module SVIII - Summary of the Safety Concerns

There are no safety concerns recognised for Capsaicin.

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

Not applicable.

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable. No post-authorisation efficacy studies with Capsaicin have been planned.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned with the reference medicinal product.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for:

- **Zacin (capsaicin) 0.025% w/w cream**
- **Axsain (capsaicin) 0.075% w/w cream**

This is a summary of the risk management plan (RMP) for Zacin (capsaicin) 0.025% w/w cream and Axsain (capsaicin) 0.075% w/w cream (herein also referred to as Capsaicin). The RMP details important risks of Capsaicin, how these risks can be minimised, and how more information will be obtained about Capsaicin's risks and uncertainties (missing information).

Capsaicin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Capsaicin should be used.

Important new concerns or changes to the current ones will be included in updates of Capsaicin's RMP.

I. The Medicine and What It is used for

Zacin (capsaicin) 0.025% w/w cream is authorised for the symptomatic relief of pain associated with osteoarthritis (see SmPC for the full indication). It contains Capsaicin as the active substance and it is administered topically.

Axsain (capsaicin) 0.075% w/w cream is authorised:

- For the symptomatic relief of neuralgia associated with and following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed;
- For the symptomatic management of painful diabetic peripheral polyneuropathy (see SmPC for the full indication).

It contains Capsaicin as the active substance and it is administered topically.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Capsaicin, together with measures to minimise such risks and the proposed studies for learning more about Capsaicin’s risks, if any, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Capsaicin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Capsaicin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

There are no safety concerns recognised for Capsaicin.

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Capsaicin.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Capsaicin.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

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Annex 5 – Protocols for proposed and ongoing studies in RMP part IV

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Annex 7 – Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Not applicable.

Annex 3 – Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.

Annex 7 – Other Supporting Data (Including Referenced Material)

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Annex 8 – Summary of Changes to the Risk Management Plan over Time

Not applicable.